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Original Articles

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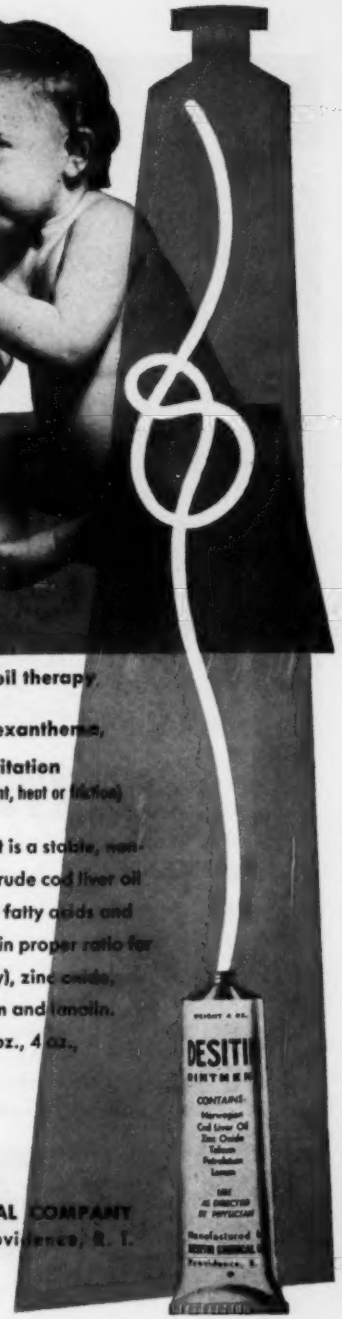

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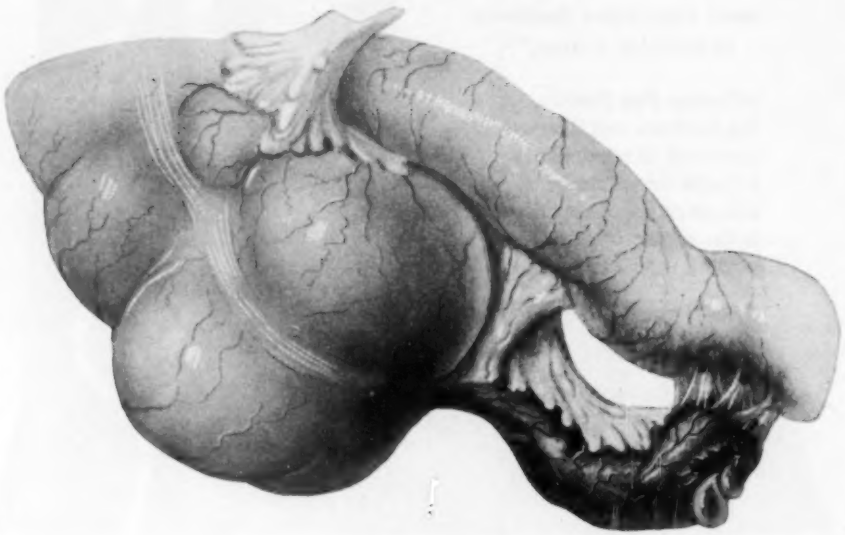

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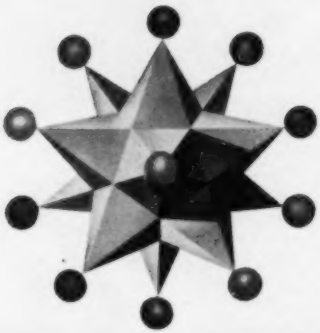

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BULLETIN OF
THE NEW YORK ACADEMY
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THE PORTACAVAL SHUNT FOR PORTAL HYPERTENSION WITH SPECIAL REFERENCE TO CIRRHOSIS OF THE LIVER*

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Five years ago at a Stated Meeting of the Academy of Medicine in a symposium on portal hypertension, Franklin Hanger discussed criteria for differentiating the various lesions giving rise to the arresting symptoms of ascites and gastrointestinal bleeding. Allen O. Whipple[1a] in a discussion of portal hypertension classified cases in two groups in accordance with the site of portal block, namely: 1) intrahepatic; for example, due to cirrhosis of the liver, or, 2) extrahepatic; cases in which the liver is normal but the portal hypertension results from a block in the portal vein or its radicals outside of the liver.

Hematemesis, the result of ruptured esophageal varices secondary to portal hypertension, Dr. Whipple stressed as the dreaded omen of serious pathology. And finally, to emphasize the need for an effective method for dealing with portal hypertension, I quote him as follows: "For many

* Presented at The New York Academy of Medicine, Friday Afternoon Lecture Series, February 16, 1951. From the Department of Surgery, Presbyterian Hospital, New York.

years one of our most discouraging follow-up problems in our Spleen Clinic at the Presbyterian Medical Center has been that of dealing with recurring hemorrhage in patients who had had a splenectomy for congestive splenomegaly or Banti's syndrome."

The rationale of the portacaval shunt for the relief of portal hypertension was discussed. We[1b] presented the results in fourteen cases in which either the portal vein or the splenic vein had been employed in the establishment of the shunts.

It is my pleasure at this time to discuss portacaval shunt in the light of increased experience with the operation. As would be expected, an experience which has, over a five year period, been expanded from fourteen cases to 140 cases affords a sufficient lapse of time to answer a few questions and a breadth of experience provocative of new questions.

At the outset we sought an early answer to one question which we considered of extreme importance. This question has long since been answered, namely, that the successful establishment and maintained patency of a portacaval shunt, employing either the portal or splenic veins, will prevent the recurrence of gastrointestinal hemorrhage due to portal hypertension. This conclusion has been arrived at on the basis of careful follow-up and necropsy observations.

The rationale of the portacaval shunt for the relief of portal hypertension has been adequately corroborated by portal pressure measurements made at the operating table before and after the establishment of shunts. As is now well understood, in portal hypertension the establishment of a portacaval shunt, e.g., an anastomosis of the portal vein itself to the vena cava or the splenic vein anastomosed, end to side with the left renal vein following splenectomy, for example, creates a shunt with a low resistance to blood flow. Under these circumstances, a large volume of blood will pass from the relatively high pressure portal system directly into the low pressure caval system via the shunt. This, of necessity, results in a marked reduction of the portal pressure.

Some idea of the magnitude of pressure drop in the portal system following the establishment of portal vein to vena cava and splenorenal types of portacaval shunts may be obtained from Table I. All of these patients had portal hypertension secondary to cirrhosis of the liver and had given a history of repeated attacks of gastrointestinal bleeding. All cases as noted had x-ray evidence of esophageal varices. The pre-shunt

TABLE I—EFFECT OF SHUNTING UPON PORTAL PRESSURE AND UPON ESOPHAGEAL VARICES

Patient	*Port. (mm.) Pre. Sht.*	*Pres. Saline Post Sht.*	*Dif.*	*Type Anas.*	*X-Ray Evid. Eso. Pre. Op.*	*Va. Po. Op.*
Capobianco*	465	190	(270)	PV.VC	3+	0
Mead*	565	220	(345)	PV.VC	3+	0
Nallon	460	190	(270)	SR.ES	2+	0
Hamilton*	330	230	(120)	PV.VC	2+	0
Pottinger	450	240	(210)	SR.ES	2+	0
Tennant	290	240	(50)	PV.VC	1+	0
Scarritt*	380	205	(75)	PV.VC	2+	0
Stone	480	225	(255)	PV.VC	3+	0

* Side to side anastomosis.

portal pressures taken at operation varied from 290 mm. of water to 565 (average 430 mm.), whereas, after the establishment of shunts there was an average fall of 200 mm. of water. The highest portal pressure noted following operation, namely, 240 mm. of water (two patients) is well below the lowest pressure ever recorded on any patients giving a history of attacks of gastrointestinal bleeding. Though the splenic vein averages somewhat smaller in calibre than the portal vein, it should be observed that the splenorenal shunts performed on Nallon and Pottinger resulted in a 270 and 210 mm. of water fall in portal pressure, respectively. This is a pressure fall which compares favorably with the portal vein to vena cava anastomoses. Confirmatory evidence of the sustained effect of the shunts in lowering portal pressure is the disappearance of x-ray evidence of esophageal varices and freedom from attacks of gastrointestinal bleeding subsequent to operation in these cases.

PORTAL HYPERTENSION AND ASCITES

That chronic portal hypertension per se does not cause ascites is an observed fact. For example, a severe grade of portal hypertension may exist for years in cases having normal livers in which the portal block is extrahepatic without the patient ever having ascites. The facts are that in our entire series of cases with portal hypertension due to

extrahepatic portal block there were no patients with chronic ascites. There was the occasional case, however, in which a mild, transitory ascites occurred following a severe hemorrhage from a ruptured esophageal varix.

Ascites becomes a problem for control in cases of portal hypertension due to cirrhosis of the liver. Yet, interesting enough, there is a high percentage of cirrhosis cases which have x-ray evidence of severe portal hypertension, and give a history of repeated attacks of gastrointestinal bleeding who have never had ascites. There is a sizeable group (25 per cent in our operated series) who had ascites and also gave a history of attacks of gastrointestinal bleeding. And, finally, there is a fairly large number of cirrhosis patients having ascites who give no history of bleeding but quite a few of whom may have demonstrable evidence of esophageal varices. In justice to the role of portal hypertension as a co-factor in the origin of ascites, it must be stated, however, that in no instance at operation upon cirrhosis patients have we failed to demonstrate the presence of portal hypertension by actual measurement of the portal pressure at the time. As a corollary to this is the fact that ascites has been regularly relieved following the establishment of portacaval shunts. We hasten to state, however, that whereas the shunting operation is the treatment of choice for patients with cirrhosis who have hemorrhaged, those having ascites only are frequently relieved by strict medical-dietary management.

There is no more stimulating chapter in medicine than the recent advances in our understanding of the liver, particularly in respect to cirrhosis and its medical management. The scope of this paper does not permit a detailed review of these fascinating approaches to new horizons. All are now familiar, however, with the promptness and surety with which modern medical management brings back compensation to the average decompensated, cirrhotic liver frequently with a return of the patient to a life of usefulness.

Even so, regrettable to state, after a decade of experience with the modern medical regimen for the management of cirrhosis, follow-up evidence points to the conclusion that there has been no reduction in the incidence of hemorrhage in cirrhosis cases. The more serious question arises whether we may not even expect an increased incidence of hemorrhage. This is in consideration of the fact that now with the modern advances in medical management, patients with more severely

damaged livers are being successfully nursed through the crisis of decompensation.

Accepting the current conception that healing with fibrous tissue deposit sets the pattern for the portal hypertension to follow, it seems but logical that the severity of the portal hypertension will be in direct proportion to the degree of liver damage preceding. Therefore, if in the future we continue to save a higher percentage of cases having badly damaged livers, it of necessity follows that the percentage incidence of hemorrhage, the result of severe portal hypertension, will rise in comparison with the incidence of former years. However this be, the current incidence of approximately one-third of all cirrhosis patients becoming victims of recurring attacks of gastrointestinal hemorrhage poses a serious problem in management.

The urgency of developing an efficient surgical technique for the care of this sizeable group of cirrhosis cases is evident from the mortality reports on such cases. For example, Arthur Patek tells me that in his series of cirrhosis cases the incidence of hematemesis was 33 per cent. Furthermore, 50 per cent of the cases having hematemesis died within one year of their first attack.

An untimely death from sudden hemorrhage or the initiation of "wasting ascites," with its resulting lingering death, is doubly unfortunate for the following reasons: 1) The liver function in these patients at the time of their first symptoms of severe portal hypertension is often amazingly good. This finding has been emphasized by many and lends support to the concept of portal hypertension being the result of healing (scar tissue contraction), and the good liver function the result of liver cell regeneration, as is regularly confirmed by liver biopsy. 2) They comprise a very sizeable proportion of the entire group of cirrhotics and as a group represent the acme of achievement and failure for the modern regimen of medical management. We say achievement because they are usually patients having very severe liver damage initially who have been carefully shepherded through a serious phase of liver decompensation, healing, and finally liver cell regeneration to the point of recovering remarkably good liver function. The subsequent development of contraction of excessive scar tissue which gives rise to grave portal hypertension in such cases marks a point of certain decline for the patient. Whether such a patient dies with the first attack of hemorrhage or not, the doctor's efforts will have been wasted for, from this point on,

the liver will progressively deteriorate as the result of recurring hemorrhages or "wasting ascites." Analysis of the case histories of our operated cases reveals positive evidence of progressive liver deterioration following the onset of severe portal hypertension in the majority of the cases. The delay in bringing these cases to early operation has, we believe, more than any other single factor affected the mortality rate following the shunting operation in our series of cases.

At the outset we adopted a broad basis of acceptance for the shunting operation to include poorer risk patients having severe portal hypertension of long standing. We realized that such a surgical philosophy would offset any possible percentage-wise reduction in operative risk as the result of improved surgical management. We preferred, however, to save more lives over the years pari passu with improvement in surgical management rather than to deny the chance of surgery to those who were doomed to die without it. But, of even more importance to future progress, our policy of a broad basis of acceptance has resulted in the accumulation of two substantial groups of operated cases for comparative analysis as follows: Group I—Cases classified as good operative risks on the basis of a clinical evaluation of the status of the liver. Shunts were established in fifty-two cases belonging to this group. There were six postoperative deaths (11.5 per cent). Group II—Cases classified as poor operative risks embracing patients who presented a history of long-standing, severe portal hypertension with marked deterioration of liver function. Shunts were established in fifty cases belonging to this group. There were 16 postoperative deaths (32 per cent), representing a salvage of 68 per cent in this desperate, otherwise hopeless group.

Analysis of these postoperative deaths is informative. Liver failure was considered the primary cause of death in 62.5 per cent of the cases belonging to Group II, e.g., ten of the sixteen postoperative deaths, whereas the liver was considered the primary cause of postoperative death in but one of the six postoperative deaths belonging to Group I.

We need not go further in our death analysis to point a way to real future progress and fortunately many medical men are already in the vanguard. This embraces a simple principle of evaluating cirrhosis patients for the shunting procedure as soon as they have developed unmistakable evidence of severe portal hypertension, as for example, an attack of gastrointestinal hemorrhage, the cause of which is confirmed by x-ray evidence of the presence of esophageal varices. If this simple

principle were carried out promptly by all physicians who attend patients having cirrhosis of the liver, it would be possible to perform the shunting operation at a considerably reduced risk. Such a policy on the part of the medical men would largely eliminate the late, poor risk patients who were classified in Group II of our series. The fact that 62.5 per cent of the postoperative deaths in Group II occurred as the result of liver failure contrasted to but one death due primarily to liver failure in the fifty-two cases belonging to Group I serves to emphasize the possibilities of such a policy.

Having demonstrated in our series of operated cases what it means in the saving of lives to have patients with cirrhosis who have developed the complication of severe portal hypertension referred early for the shunting operation, we will now discuss the responsibilities of the surgeon.

We early realized that to achieve clinical success with the shunting operation would require circumvention of many difficulties some of which are extremely complex and poorly understood. The discouraging facts were that up to the early forties, just a few years before undertaking our study, reports continued to appear in the literature admitting hospital mortality rates from 30 to 50 per cent following relatively simple operative procedures such as splenectomy and omentopexy in patients having cirrhosis of the liver.

By 1944, however, when we undertook our study there had been important advances which we believed could be employed to favorably affect the clinical success of portacaval shunts as follows: 1) Sufficient time had elapsed for the good results of the Patek regimen for the treatment of cirrhosis of the liver to become apparent. 2) Evidence had accumulated in support of the fact that a cirrhotic liver well fortified with proteins, carbohydrates and vitamins, if protected against anoxia, is far more resistant to decompensation following surgery than livers not so protected. 3) The availability of whole blood, plasma and finally, human albumin for the quick correction of anemia, restoration of blood volume and restitution of depleted proteins. 4) Achievement of potential control of infection, control of blood clotting (culminating in a safe method of regional heparinization) and better control of postoperative abdominal distention – all-important factors favoring success with intra-abdominal venous shunts. 5) Advances in the administration of anesthetics which, with new anesthetic agents (cyclopropane), promoted the maintenance of a higher blood pressure with maximum oxygenation

of the blood during operation which in turn, with the availability of adequate quantities of banked blood, afford protection against the occurrence of shock.

The process of integrating the above advances into a plan for the surgical management of cirrhosis cases for the shunting operation lent assurance to our early successes. It was not, however, until our experience had broadened to include the many clinical patterns of the disease that we realized the true magnitude of the problems in surgical management.

It is true we were able to register consistent progress in our ability to operate successfully upon cases of cirrhosis presenting evidence of more severely damaged livers. But, it early became a matter of increasing concern that progress was uncertain in coping with certain poorly understood complications. For example, in cases of cirrhosis complicated by ascites some early successes had encouraged us to believe that patients meeting certain requirements based upon the usual liver chemistry and function studies may be expected to go through the shunting procedure without undue risk.

Today, in the light of more experience, patients with cirrhosis having "wasting ascites" are selected for operation only after their water metabolism and ability to excrete sodium are carefully evaluated on balanced studies. It is only by careful studies of this kind that we may be forewarned of those patients who are likely to succumb following the shunting operation because of water and sodium retention. The above derangement has accounted for 23 per cent of our postoperative deaths in the past. The hydrophilic state which exists to an extreme degree in a sizeable group of cirrhosis patients is becoming better understood. There have been studies made by Ralli,[2] Labby,[3] Shorr and his coworkers[4] to show that in liver failure there may be an increased accumulation of antidiuretic substances which suggests an alteration in hormonal control of the renal tubules. Certainly, in our current plan of conducting balanced studies pari passu with the upbuilding program for improving the liver, evidence has accumulated to confirm the observation of others, namely: that diuresis with the excretion of sodium does improve with improvement of liver function. In view of the fact that serum albumin depletion, as a possible factor in ascites, can now be promptly overcome by the parenteral use of human albumin, the ultimate evaluation of operative risk in such cases rests upon the degree of

diuresis and excretion of sodium per twenty-four hour period that a given patient can finally achieve.

Evidence has already accumulated employing the above program of preparation and evaluation to restore our confidence that a high percentage of patients having "wasting ascites" with evidence of severe portal hypertension may now be shepherded safely through a shunting procedure. At this point, however, we wish to emphasize once again that only "treatment failures" should be considered for operation. By treatment failures we mean failure to reduce ascites after many months of an energetically applied medical regimen for cirrhosis. This is meant to include restriction of sodium to less than one gram a day.

It is true there are patients having ascites refractory to medical management who are end-stage cirrhotics having, at best, but a few weeks or months to live. These patients having evidence of severe liver damage, often chronic unremitting jaundice, in our experience have been more frequently encountered in the older age group. By far the greatest number of cases refractory to medical management, however, are patients having severe portal hypertension as the important co-factor in the persistence of their ascites. The liver function tests in this group are often remarkably good. Again and again we have successfully established portacaval shunts in cases belonging to this group and restored the patient to a life of usefulness. In fact our oldest follow-up case is a patient who had been treated in several of our good clinics without relief of his ascites. A portacaval shunt was established in this patient six years ago. His ascites was relieved; he was able to resume his former active work as a timber estimator and has remained well and active ever since. It was interesting to note at a recent examination of this patient that his liver function tests were improved approximately 40 per cent over their preoperative levels. From all appearances this man, who is now fifty-six years of age, will continue to have satisfactory liver function for years to come. In conclusion, it is our opinion that the portacaval shunt has a most useful role in the treatment of ascites providing extreme care is employed in the selection and preparation of cases for operation.

Hemorrhage as a Complication in the Shunting Operation

As was the case with ascites, as our experience broadened we became increasingly aware of the fact that there were present in cirrhosis cases complex factors contributory to the initiation of hemorrhage, the ex-

istence of which we did not appreciate early in our experience. In the 102 cirrhosis cases in which the shunting operation was performed, there were eight postoperative deaths due to hemorrhage. Technical errors accounted for three of the deaths. The cause of hemorrhage in the remaining five cases will be made the subject of discussion.

Hemorrhage as the result of technical errors we rightfully expected to eliminate with improvement in our technical performance of the shunting procedure. We became prepared to deal effectively with the sudden occurrence of hemorrhage, the result of rupture of esophageal varices. The answer to this problem for the emergency control of hemorrhage was the development of a satisfactory and efficient nasogastric tube esophageal balloon assembly for prompt esophageal tamponage. For the tendency to hemorrhage as the result of an elevated prothrombin time, we counted upon hykinone for its correction. For the occasional case of extreme hypersplenism with an extremely low platelet count we used freshly banked blood immediately before operation.

Finally, all the above factors having been accounted for, there was the occasional patient who developed, during operation, hemorrhage which could not be satisfactorily controlled by clamp, ligature or suture. The sudden appearance of bleeding in a previously dry wound in such cases offered excuse for much speculation and concern. The absence of preoperative evidence of delayed clotting or other bleeding dyscrasias in such cases created a distinct element of surprise. The fact that bleeding occurred in these patients who received the same careful attention to the avoidance of anoxia, supportive measures, including blood replacement, as did the other cases of cirrhosis, suggests the presence of circulating vasotrophic substances in excessive amounts in such cases.

Ephraim Shorr and his co-workers[5] have demonstrated the presence of a high concentration of vasodepressor material (VDM) in the liver and blood of rats having nutritional cirrhosis. The substance has also been identified as occurring in variable concentrations in cases of human cirrhosis. VDM has been identified as an iron-protein compound known as Ferratin. Its formation is under the control of a specific enzyme system primarily in the liver which functions, under anoxic conditions, to produce large quantities of VDM. A second enzyme system in the liver, which under oxidative conditions functions normally to inactivate VDM, is markedly impaired in cirrhosis of the liver according to these

investigators to account for the rise of VDM in the circulating blood of cirrhotics beyond physiological, homeostatic, levels. They went further to demonstrate that VDM produced a marked antidiuretic effect when infused in the veins of normal dogs.

Dr. Shorr and his associates made the above observations as a part of their far-reaching studies of experimental shock. They have detected and investigated a renal factor in circulatory homeostasis affecting particularly the compensatory phase of shock. For a comprehensive presentation of their studies I refer you to their recent article entitled "Hepatorenal Factors in Circulatory Homeostasis."[8]

There are striking features of similarity between the behavior of animals having experimental (nutritional) cirrhosis and certain human cirrhotics when exposed to operative trauma. Outstanding are the common tendencies to poor tolerance of anesthetics disposing to anoxia and vasomotor hyporeactivity, disposing to an early fall in blood pressure. We have frequently observed the lack of this normal protective mechanism upon making the skin incision for a shunting procedure in cirrhosis cases; the smallest blood vessels one can see and many too small to see bleed profusely upon cutting.

The demonstration of Shorr and his co-workers of the presence of large quantities of a vasodepressor material, which they have identified as Ferratin, in the circulating blood of patients having decompensated livers due to cirrhosis has alerted us to the necessity of taking this factor into consideration.

Since the formation of vasodepressor substance (Ferratin) has been shown to take place in the liver at a more rapid rate under anoxic conditions, emphasis is placed upon the following measures in the surgical management of cirrhosis cases for the shunting procedure: 1) The oxygen carrying potential of the blood is brought to a high peak of normal before operation. Based on blood volume determinations, the red blood cell mass is brought up to 38 to 40 cc. per kilo body weight by transfusion. Or, if the plasma volume be already high, as is often the case in cirrhotics, only red blood cells are given. 2) Respiratory depressants are omitted in the preoperative medication. 3) Cyclopropane anesthesia, well administered, employing an endotracheal tube, is decidedly the choice of anesthetics for patients having cirrhosis of the liver. 4) A continuous recording of blood pressure is highly desirable in patients showing a tendency to bleed. We employ a Lilly manometer for this purpose

connected with a fine plastic catheter introduced into the brachial artery. From these tracings can be obtained not only the blood pressure but the relative state of vasomotor tone as reflected by the position of the dicrotic notch on the pulse tracing. In addition, a coincident EKG recording is made which is particularly of value when operating upon patients of the older age group. 5) Adequate equipment and provision for the rapid administration of blood under pressure if necessary. We have repeatedly noted a distinct lag in blood pressure rise following even the rapid administration of blood intravenously in patients with cirrhosis who show a tendency to bleed. In contrast, probably due to the initiation of the aortic reflex mechanism, a prompt rise in blood pressure results from the administration of blood intra-arterially.

Desiring most of all to keep the blood pressure stabilized as a protection against anoxia of the liver and shock, we have devised a special needle for intra-arterial transfusion. Before the operation is started this needle is placed in the femoral artery and connected with a pressure circuit in readiness for quick use if the occasion arises. In the average case, however, the intravenous route serves adequately for blood replacement during operation. Citrated blood is employed and the anticoagulant action of sodium citrate is carefully neutralized by the administration of calcium gluconate. Frequent clotting determinations are made on the blood during operation and if it is found to be elevated, as rarely is the case, protamin in 50 mg. doses is administered intravenously. As a rough guide to adequate blood replacement hematocrits are taken during operation. But, in special cases, in addition, blood volume determinations are made during operation to keep an accurate check on the plasma volume during periods of massive blood replacement. 6) Adequate blood bank facilities. It goes without saying that our operative mortality due to hemorrhage (less than 8 per cent in the 102 cases) could never have been achieved without the blood bank.

If we are to accept the conclusions of Dr. Shorr and his associates, we must attach another important role to the use of transfusions during the shunting operation upon cases having cirrhosis of the liver, namely, the diluting effect of massive blood replacement in effecting a reduction in the concentration of VDM in the circulating blood. This is a possible factor of no mean importance when one considers that blood replacement may exceed the total blood volume of the patient. Shorr and his coworkers have shown that high blood concentrations of VDM in cirrhosis

exerts a strong antidiuretic effect. As further evidence that the concentration of VDM may be markedly reduced following massive transfusions is the fact frequently observed that the kidneys promptly put out urine following operation. This is well illustrated in the case of a fifty-six year old South American physician on whom a side to side portal vein to vena cava anastomosis was performed three days ago. This patient had ascites and gave a history of repeated attacks of gastrointestinal bleeding. At operation he had far more bleeding than the average case. He received 9000 cc. of blood during the procedure. Two hours after operation he was catheterized and 400 cc. of urine was obtained. His urine output thereafter has averaged 50 cc. per hour which compared favorably with his preoperative output except on the days that he received mercuhydrin.

There were three cardiac deaths in the 102 cases of cirrhosis in which shunts were established. All of the patients were in the late fifties as to age. We are no longer academic when it comes to the question of digitalization in these patients. It is our considered opinion that there are not infrequently evidences of heart strain in the older age group during the performance of the shunting procedure and if such evidence develops, we are not averse to quick digitalization of the patient during operation. Frequent EKG tracings while the patient is on the operating table is a valuable guide to the heart action.

Indications for the Different Types of Portacaval Shunts

The portal vein to vena cava anastomosis and the splenic vein anastomosed end to side with the left renal vein following splenectomy are the veins most commonly employed by us in the establishment of portacaval shunts. The portal vein to vena cava type of portacaval shunt is regularly available for patients having portal hypertension due to intrahepatic block, as for example, cirrhosis of the liver. Whereas, in cases of portal hypertension due to extrahepatic portal block, the site of block invariably in our experience has been in the portal vein itself, rendering it unfit for shunting purposes. In such cases, the splenic vein is the one best chance for the establishment of a portacaval shunt via the left renal vein. Sad to relate, there yet are many cases of post-splenectomy bleeders belonging to the extrahepatic group in which the one best vein for this group was unnecessarily sacrificed in doing a splenectomy under the false hope that splenectomy cures gastrointestinal bleeding.

We have attempted to employ the mesenteric veins for shunting purposes in this unfortunate group of post-splenectomy bleeders in the past. Likewise we early employed femoral vein grafts to bridge the distance between the stump of the splenic vein and the left renal vein. The overall results were disappointing. Renewed hope for more uniform success, employing lesser veins for shunting purposes, has come with the recent development of a technique for regional heparinization to protect the shunt against thrombosis during the healing period of the anastomosis.

The question has been logically asked many times, what factors decide whether the portal or splenic veins should be used for shunting in cases in which both are presumably available for use, as for example, in cirrhosis cases. Since the primary purpose of the shunting operation is to protect patients from death due to ruptured esophageal varices, the question resolves itself to the employment of that vein which gives the highest percentage of cure with the least operative risk to the patient. As is but logical to expect, it has taken some time to evaluate the relative merits of the portal vein to venacaval and splenorenal types of portacaval shunts. For example, a comparative analysis was made in thirty-eight cases of cirrhosis in which the portal vein was employed with thirty-eight cases of cirrhosis in which the splenorenal type of portacaval shunt was employed. Whereas, the postoperative mortality was the same in each group, the follow-up mortality was nine patients in the splenorenal group compared to only three follow-up deaths in the group in which the portal vein was employed for shunting purposes. Furthermore, death was due to recurring gastrointestinal hemorrhage in five of the nine patients having splenorenal shunts as against no deaths from hemorrhage in the portal vein to vena cava group of portacaval shunts. A necropsy was performed in three of the five patients having splenorenal shunts and the shunt was found to be occluded in each instance. In all of our subsequent follow-up experience with the portal vein to venacaval type of portacaval shunt, there has been only one death from hemorrhage and that in a patient having partial thrombosis of the portal vein.

Whereas, as stated previously, the average splenorental shunt will handle sufficient blood to reduce the portal pressure well below hemorrhage levels, we cannot count upon this shunt maintaining its patency to the same degree as has been demonstrated when employing the portal vein for shunting purposes. On the other hand, we may expect a con-

siderable reduction in our percentage of follow-up failures with the splenorenal shunt in the future because of the employment of regional heparinization. Early in 1950 we worked out a technique employing a fine plastic tube for the introduction of a continuous heparin drip during the postoperative healing period of the shunt. Upon completion of a splenorenal shunt, e.g., the plastic tube is introduced into the inferior mesenteric vein and secured with two silk ligatures. The tip of the plastic tube is advanced to a point just short of the splenic vein. The other end is brought out of the wound and connected for a continuous heparin drip.

It is our opinion that the most likely time for a splenorenal shunt to become thrombosed is during the period of postoperative distention before the anastomosis site has become healed. Now with the employment of regional heparinization we can prove whether the shunt is open or not at the end of the healing period before the plastic tube is removed. This is accomplished by doing differential blood clotting times on a venous blood specimen taken from the arm and a second specimen withdrawn from another plastic catheter which has been advanced up the vena cava via the femoral vein to just above the left renal vein. A higher clotting time on the venacaval sample of blood indicates that the shunt is patent. The clotting time usually differs at a three to one ratio. As a check on the clotting time, differential oxygen content may be determined on the two venous specimens of blood. A higher oxygen content for the sample of venacaval blood indicates a mixture of portal blood thus proving the shunt to be patent.

Even with the advantages of regional heparinization, in our opinion the splenorenal shunt will never become the sure proposition for the relief of hemorrhage that the portal vein to venacaval type of portacaval shunt has proven to be. It is fortunate that the portal vein is available for use in all cases of portal hypertension due to intrahepatic block, including the cirrhosis group. Following the establishment of this type of portacaval shunt the enlarged spleen becomes progressively smaller with gradual improvement in the platelet count or other evidences of hypersplenism.

We prefer a side to side arrangement of the anastomosis of the portal vein to the vena cava. In those cases having a large caudate lobe of the liver, the above arrangement can be maintained by bridging the distance between the portal vein and vena cava, employing a short segment of

femoral vein. The side to side arrangement is preferable to the end to side anastomosis because it permits portal blood to continue its flow to the liver after opening the shunt, should the pressure relations be conducive to flow. Aside from the higher degree of certainty of a successful shunt when employing the portal vein compared to the splenic vein, the operation is technically less tedious and difficult to accomplish in the average case.

Follow-Up Observations in Cirrhosis Patients Following the Establishment of Portacaval Shunts

There is no apparent reason to assume that a shunting procedure should have any specific beneficial effect upon the cirrhotic liver. On the other hand, neither should there be any deleterious effects. Dr. Bradley and his associates have done blood flow and oxygen utilization studies on the liver in a few patients before and after the establishment of shunts. A preliminary report on the work done so far would indicate that oxygen utilization by the liver is not diminished or impaired by the establishment of portacaval shunts.

The follow-up death analysis of eighty cases of cirrhosis having the shunting procedure is as follows:

1. There were five cases who died of hemorrhage; roughly a 6 per cent failure for the shunting operation. There was only one portal vein to vena cava anastomosis in this group.

2. Liver failure — six cases. These patients lived for varying periods up to four years following operation.

3. Other causes — five cases, listed as follows:

Pneumonia	1
Pulmonary embolism	1
Ruptured peptic ulcer	1
Virus hepatitis	1
Nephritis	1

The majority of the living patients are leading active lives. Many of them are engaged in earning their livelihood. There has been amazing clinical improvement in many patients since operation, and through liver chemistry studies, there has been evidence of improvement in liver function in some.

It may be stated in conclusion that our experience would indicate the

primary role of the portacaval shunt as follows: 1) to protect patients from an untimely death due to hemorrhage; 2) to protect livers in cirrhosis cases from the deleterious effects of recurring hemorrhage or wasting ascites and thus afford an opportunity for healing and regeneration of new liver cells under the favorable aegis of modern medical management.

Summary

The rationale of the portacaval shunt for the relief of portal hypertension with the results in an operative experience embracing 140 cases is presented. The cases of portal hypertension are classified in accordance with whether the site of portal block is within the liver, as for example, due to cirrhosis or extrahepatic, as for example, due to obstruction in the portal vein itself. Of the 140 cases in which shunts were accomplished there were 102 cases of cirrhosis of the liver as compared to thirty-eight patients in whom the site of portal block was extrahepatic.

Factors influencing operative risk are discussed which reflect the importance of the functional status of the liver in relation to the duration of the disease and the deleterious effects upon the liver of long-standing portal hypertension. For example, the 102 patients having cirrhosis of the liver operated upon are classified in two groups as follows: *Group I*, to include cases having relatively good livers as evaluated by liver function studies. *Group II*, embracing cases presenting evidence of markedly impaired liver function, frequently the result of the deleterious effects of long-standing, severe portal hypertension. There were six postoperative deaths (11.5 per cent) in fifty-two cases classified as Group I, with only one death ascribed to liver failure. In fifty cases having severely damaged livers classified in Group II there were sixteen postoperative deaths in ten of which liver failure was the cause of death. On the credit side this represents a 68 per cent salvage in that group of patients otherwise doomed to die in a matter of a few weeks or months.

The fact that 62.5 per cent of the postoperative deaths in Group II cases were due to liver failure in contrast to but one death due to this cause in the fifty-two operated cases belonging to Group I is most important. It points unmistakably to one way of greatly reducing operative risk in the future, namely, a simple rule of evaluating cirrhosis patients for the shunting procedure as soon as they develop unmistakable evidence of portal hypertension. The over-all operative mortality for the

entire series of 140 cases is 17.8 per cent. In the thirty-eight cases having extrahepatic block, there were but three postoperative deaths.

A plan of surgical management is presented with particular reference to the preparation of patients with cirrhosis having ascites for operation. The prevention of anoxia and shock during operation, and postoperative care are discussed. The follow-up results in eighty cases of cirrhosis are presented.

REFERENCES

1a. Whipple, A. O. Rationale of portacaval anastomosis, *Bull. N. Y. Acad. Med. 22*:251-53, 1946.

b. Blakemore, A. H. Portacaval anastomosis: a report on fourteen cases, *Bull. N. Y. Acad. Med. 22*:254-63, 1946.

2. Ralli, E. P., Robson, J. S., Clarke, D. H. and Hoagland, C. L. Factors influencing ascites in patients with cirrhosis of the liver, *J. clin. Invest. 24*:316-25, 1945.

3. Labby, D. H. and Hoagland, C. L. Water storage and movements of body fluids and chloride during acute liver disease, *J. clin. Invest. 26*:343-53, 1947.

4. Baez, S., Mazur, A. and Shorr, E. Hepatorenal factors in circulatory homeostasis; antidiuretic action of hepatic vasodepressor, V.D.M. (ferritin), *Amer. J. Physiol. 162*:198-212, 1950.

5. Shorr, E. Hepatorenal vasotropic factors in experimental cirrhosis, *Transactions of the Conference on Liver Injury, 6*:33-39, 1947.

6. Shorr, E., Zweifach, B. W., Furchgott, R. F. and Baez, S. Hepatorenal factors in circulatory homeostasis; tissue origins of the vasotropic principles, VEM and VDM, *Circulation 3*:42-79, 1951.

THE INFLUENCE OF ACTH ON THE SENSITIZING AND IMMUNIZING ANTIBODIES OF INHALANT ALLERGY*

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THE mechanism whereby ACTH and cortisone exert their influence on a wide variety of medical conditions, including hay fever and asthma (Bordley and others,[1] Randolph and Rollins,[2] Samter,[3] Carryer et al[4] and Rose[5]) is unknown and subject to much speculation. Several theories have grown out of early observations, largely on experimental animals. The first is that the hormones effect a release of preformed antibodies from lymph cells within some six to nine hours and that these immune bodies exert a favorable influence on the host. The second hypothesis holds that the hormones alter the *rate* at which antibodies are formed following an antigenic stimulus. The third concept is that the union of antigen and antibody is in some way inhibited. Still another contention is that the site of action of the hormones is on some stage beyond the antigen-antibody combination, such as the elaboration of inflammatory substances or the susceptibility of the effector cells to these irritants. Since evidence can be found in the current literature on both sides of these several theories and inasmuch as no controlled studies on the relation of the hormones to the fixed and circulating antibodies of the allergic patient have as yet been published, appraisals have been made of both the sensitizing and the protective (or blocking) antibodies of an inhalant-allergic woman who received ACTH for some months. The relation of our findings to those in literature, as well as some speculations as to the site of action of the cortical hormones, will also be presented.

MATERIALS AND METHODS

The subject was a woman of twenty years who gave a history of perennial, widespread, atopic dermatitis with summer exacerbations for

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over ten years and who gave definite clinical and intracutaneous responses to the pollens of trees, grasses and ragweed as well as to the epidermis of dog and of horse. Asthma and summer hay fever were of secondary importance. She had received no specific immunization against timothy pollen for a year, and injections with ragweed pollen had been discontinued two years before the present investigation because of unsatisfactory clinical control of her complaints.

During the two days preceding her first injection of ACTH, she was tested by a controlled conjunctival method[6] which revealed the thresholds of susceptibility for timothy and ragweed pollens. At the same time, a sample of her serum was prepared. These tests were repeated periodically in the first two and one-half months that she underwent ACTH therapy, the dosage being determined by Dr. Horace S. Baldwin empirically and according to her clinical needs. Treatment commenced at noon on June 8, 1950, and continued beyond the termination of these immunological studies on August 9. That the patient received adequate amounts of ACTH may be concluded from her definite clinical improvement and a reduction in circulating eosinophils from 1023 to 391 per c. mm. within ten hours after the first six-hourly injection of 20 mg. of the hormone as well as the eventual development of such side effects as Cushing's facies, glycosuria and a gain of 20 pounds in weight.

Serological titrations were of three varieties,[7] all carried out in the skin of one normal test subject who received weekly intracutaneous injections of diluted serum and of serum-antigen mixtures over a period of five weeks. Care was taken to avoid the use of any area on more than one occasion, an objective made possible by indelible markings and the fortuitous development of slight pigmentation locally after each reaction. Stability of serum specimens, glycerinated allergens and test-subject reactivity was ascertained through the deliberate overlapping of crucial serum-antigen mixtures in successive experiments. Whereas each reactive site was created by the use of 0.1 cc. of diluted serum or of serum-allergen mixture, the twenty-four provocative tests were carried out with .03 cc. of 160-unit extract (0.1 mg. of phosphotungstic-acid-precipitable nitrogen representing 10,000 Pta-N units).

The serological techniques have been previously described[7] in detail and will be touched upon briefly here. In all instances, the end point was a threshold, or minimal, reaction. Serum specimens were freshly diluted for each set of experiments in a series of two-fold differences.

Antigens were set up in a series of two-fold concentrations from stock supplies maintained in 50 per cent glycerin. Testing began in October.

Serum dilution titrations revealed how far a specimen could be diluted and still give rise to a wheal-and-flare in normal skin when the site into which it had been injected was tested with allergen in twenty-four hours. The method reveals only the relative sensitizing potency of one as compared to another serum studied in the same experiment. Any blocking antibody present in the serum will have disappeared from the site by twenty hours[8] so that the test measures only sensitizing antibodies. These reagins are known[9] to remain fixed to the tissues as long as three months.

Neutralization of the serum may be carried out in either the native state or after the sample has been heated in a waterbath at 60°C for one hour. The result in the former case reveals how much allergen is required to exhaust the sensitizing power of a measure of the serum but it is not possible to state what proportion of the requirement is referable to any blocking antibody which happens to be present in the sample. (This antibody, which is induced by injections of allergen, will deprive the sensitizing antibody of the allergen until an excess of the latter has been added to the titration experiment. Consequently, extra allergen must be employed in order to neutralize the sensitizing power of a serum which also contains the blocking factor.) It is more satisfactory, therefore, when dealing with blood from allergen-treated patients, to supplant the older with the newer procedure of titration; viz., to measure the thermostable, blocking antibody after destroying the sensitizing antibodies by heat. A reagin-bearing serum from an untreated individual (who will lack the induced, blocking antibodies) must be "borrowed" for the experiment. The difference between its neutralization requirement in a passive transference test and that noted when the heated serum is added to an identical series of mixtures will indicate the potency of the heat-stable, blocking antibodies. Since there is no known way to inactivate or remove the latter so that the thermolabile antibodies in an immune serum can be separately evaluated by neutralization, one must rely on the serum-dilution titration for this purpose. Unfortunately, it is not as reliable as the neutralization method which can often be reproduced within one half tube of antigen-dilution.

Under ordinary conditions of pollen therapy, the height of blocking antibody production is reached within seven to ten days after a booster

dose and is maintained for at least two months. As the titer rises in the blood, the tolerance for the antigen rises in the eye and skin, so that the assumption may be made that thermostable antibodies also invade the tissues and account for their increased resistance.[7]

Findings

The institution of ACTH therapy on June 8th exerted a distinct effect on the conjunctival susceptibility of the patient for her two pollen allergens as well as for dog epidermis. Timothy pollen produced a minimal reddening of the caruncle, for example, when one drop of a 160-unit preparation was instilled into the conjunctival sac on June 6th and June 7th. The degree of increase in tolerance conferred by ACTH is indicated by the sharp rise in the eye-test curve shown on Figure 1, the provocative dose of grass extract being 16 times greater when determined on the fourteenth and twentieth days of hormone therapy. Increased ratios of tolerance amounting to fourfold were also noted for dog dander and ragweed pollen a fortnight after ACTH injections had been started, 10,240-unit solutions now being required.

Meanwhile, the circulating sensitizing antibodies for timothy and ragweed pollen, as well as for horse epidermis, remained unchanged in concentration as indicated by both the serum-dilution and the antibody-exhaustion curves of Figure 1 for the unheated serum specimens of June 22 and 28. There was no evidence for the presence of thermostable blocking antibodies against either timothy or ragweed pollen in any samples taken prior to specific allergenic injections with these pollens. In other words, when the patient's pre-ACTH bleeding was titrated in passive transference tests, no extra allergen had to be added to the serum-antigen mixtures if a volume of any of the June specimens in heated state was included in the analysis.

Specific, intracutaneous therapy for timothy pollen was now given in an intensive manner which the author has been developing.[10] The dosage was deliberately and cautiously carried slightly past the limit of clinical tolerance on each of three successive days, a cumulative dose of 5000 Pta-N units being reached. When conjunctival tests were repeated 16 days later, the values for timothy had risen another 8-fold, bringing the threshold dose to the high level of 20,480. Meanwhile the ophthalmic susceptibility remained unaltered for ragweed pollen, showing the antibody response to be specific and not nonspecifically anamnestic.

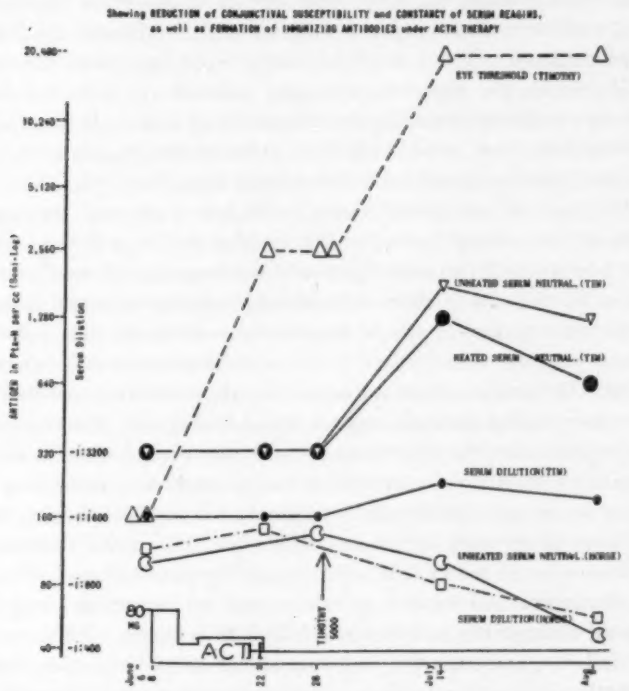

Fig. 1

Serological tests revealed the acquisition of thermostable, "protective" antibodies for grass pollen during this period, four times more antigen now being required to exhaust the pre-ACTH sample in the presence of heated serum obtained on July 14th than when the heated specimen of June 28th was involved. It will be noted that somewhat more allergen had to be used in order to desensitize the July 14th serum when it was employed in the unheated state (and without the addition of any reagin-bearing serum). This is because the sensitizing power of the pre-ACTH sample, borrowed for the estimation of blocking antibodies in the heated preparation of July 14th, was slightly less potent than that of the unheated July 14th serum. The slight rise of the serum-dilution titer for this date suggests that specific therapy with timothy

pollen had stimulated the output, not only of thermostable factors, but perhaps of extra sensitizing antibodies as well. Additional antigen required to desensitize this acquired reagin could have been the factor responsible for the higher titration end point of the unheated serum with its coexisting sensitizing and immunizing bodies. Both types of antibody had commenced to fall off in concentration by the forty-third day after timothy immunization on August ninth.

The outcome was quite different in the case of ragweed, no thermostable antibody being formed as the result of the large dose of 10,000 units which was given intracutaneously over a period of two hours, in spite of the fact that the limits of tolerance had been surpassed as shown by the development of a mild reaction of overdosage. The failure of immune response was apparent in the heated serum not only when the pre-ACTH specimen was employed for the sensitizing medium but also when another patient's reaginic serum with a very low neutralization requirement was substituted. There was a suggestion in serum-dilution studies that enhancement of reagin production took place following the antigenic stimulus but the degree was so slight as to approach the limits of accuracy of the test. (On June 7th passive transference could be achieved with a dilution of 1:3000, by June 28th and July 14th the dilutability was located at 1:6000, and by twenty-six days after ragweed therapy the endpoint was found at 1:10,000.) Thus, we not only failed to immunize but may have added somewhat to the patient's humoral sensitivity by our therapy with ragweed extract during ACTH treatment. No ragweed pollen was in the air during this period.

Throughout the entire period of observation, the sensitizing antibodies for the control allergen, horse epidermis, failed to increase. Indeed, a small reduction in reaginic activity appeared to be taking place in the patient's blood, according to both the dilution and the absorption results. This may have been due to the lack of her customary contact with horses while hospitalized and in the environs of New York City. Our failure to find these antibodies increased during immunization with two pollens emphasizes the specificity of the antibody responses, just as the immunization with one pollen failed to alter the antibody output for the other pollen. It also excludes the test-subject as an explanation for the rises noted in other curves of Figure 1.

Any influence of ACTH on the *magnitude* of these immune responses to pollens could be judged from similar immunizations given 14

control patients whose levels of allergy were comparable with that of our ACTH subject as judged by tests of the eye. Whereas their resting thresholds of susceptibility prior to "flash" booster therapy ranged between 80 and 240 (median value 160, the same as for our ACTH case), these were raised by a median ratio of 10-fold after they had received an average of 1300 Pta-units of extract in 1 to 3 visits. Since our hormonally treated subject responded to her course of 5000 units of timothy extract by a further rise of 8-fold in her conjunctival requirement, it is theoretically possible that her reaction to immunization was somewhat below normal, although very definite. The end point of 20,480 is unusually high and reflects, of course, the effect of ACTH on the original threshold value as well as the secondary influence of acquired blocking antibody.

With reference to ragweed immunization, this is the first instance among several hundreds in the writer's experience where no thermostable antibodies could be provoked by a booster dose of 10,000 units given during a number of days or weeks.[7] Interpretation of this failure is complicated by our patient's history of poor clinical response to earlier prophylactic injections of ragweed pollen, and must await the repetition of our booster dose next summer when ACTH will be withheld. In seeking an explanation for the contrasting success of timothy treatment during the administration of ACTH, two differences between the two courses of pollen extract were uncovered. For one thing, it was clear from initial conjunctival results that the young woman was sixteen times more allergic to grass than to ragweed pollen—a situation which would tend to make her more responsive to therapy with a given dose of the former. A second variable lay in the interval between pollen injection and the preceding dose of ACTH. The timothy treatments were each commenced at between 8½ and 10½ hours after a 10 mg. dose of ACTH, whereas the ragweed course was started at 3¾ hours and completed within another two hours after the dose. It is theoretically possible that the latter immunization, given at the probable peak of hormonal effect, was inhibited whereas the timothy immunization largely escaped this influence. Such a time factor might underlie the conflicting reports in the literature on antibody formation in the hormone-treated animal.

The difference in interval between the 10 mg. dose of ACTH and the pollen inoculations may also have colored the overdose reactions.

In the instance of timothy, our subject appeared to have no higher tolerance for injected antigen than did 33 control patients in her conjunctival class. Our patient did, however, manifest greater tolerance for ragweed extract than ten other control subjects with her pre-ACTH conjunctival susceptibility (2560). These patients developed systemic reactions after cumulative doses ranging from 1200 to 5500, median 3200. Our ACTH-treated subject, it will be recalled, tolerated 10,000 units before developing generalized urticaria. Whereas the ragweed extract produced manifestations only in her skin, the grass solution led to cutaneous, nasal and bronchial reactions.

Did the hormone exert a protective influence against the injected ragweed extract given at four hours whereas this inhibitory effect was lost by 8½ hours when timothy injections were commenced?

Summary and Discussion

The following summarizes our findings in an ACTH-treated woman with classical allergic eczema, hay fever and bronchial asthma. Sensitizing antibodies, which are elaborated spontaneously by allergic individuals following specific contact, continued to be present in the blood serum in the same concentrations as before hormonal therapy. Nevertheless, the susceptibility of the patient's tissues was reduced, as judged by controlled, threshold testing of her conjunctiva with three inhalant allergens on several occasions after the fourteenth day of ACTH treatment. While on maintenance doses of the hormone, the young woman was stimulated to form effective amounts of thermostable, blocking antibodies by means of a few, maximal doses of grass pollen extract. On the other hand, she failed to produce these immune bodies when ragweed pollen was selected as the booster stimulus two weeks later while still receiving hormone. An associated increase in *reagins* following these two brief intracutaneous courses was so slight as to be of questionable significance. (Some enhancement occurs in most, but not all, pollen-allergic subjects following specific injections.) The development of induced, thermostable antibodies was restricted to the allergen injected, no anamnestic formation of sensitizing or of thermostable bodies for the other pollen or for horse dander being noted.

It would appear from these observations that the hormonal control of our patient's dermatitis prior to booster therapy was associated with no change in the concentration of antibodies, either sensitizing or block-

ing, in her serum. The hormone must therefore have been acting at some point beyond the reagin-producing cells and beyond any mechanism which may be postulated for the liberation of either type of antibody. We were, at any rate, unable to support the proposal of Dougherty, Chase and White[11] that adrenal cortical activity leads to a release of preformed antibodies from lymphocytes through lysis. Their observation of a rise in circulating antibody following the giving of ACTH to previously immunized rabbits could not be duplicated by Fischel, LeMay and Kabat[12] using the quantitative precipitin method three months after immunization, or by DeVries,[13] or Bjørneboe, Fischel and Stoerk[14] who worked with the same species and analytical methods but allowed shorter periods of rest after immunization. However, Eisen et al[15] did agree with Dougherty's group in that there occurred, in previously immunized rabbits, shortly after a single dose of adrenal cortical extract, an elevation of serum antibody nitrogen amounting to about 30 per cent. This "non-specific" anamnestic rise lasted only about 12 hours and did not take place at all in animals with originally low titers. Our observations would not have caught an early, brief change of this nature since no blood was taken until the 14th day of hormonal therapy. So fleeting a shift in circulating antibodies would, in any event, fail to explain the more gradual and prolonged clinical effect observed.

From the theoretical viewpoint, there are other reasons why the non-specific anamnestic response offers an unsatisfactory explanation for the clinical control of allergy. It would have to apply to the thermostable, blocking bodies rather than to the sensitizing factors inasmuch as the latter would only enhance clinical manifestations. This implies that the hormonal benefits should be found predominantly in patients who have been previously immunized with the etiologic allergen, since the blocking bodies are usually not formed in significant amounts unless deliberate, parenteral exposures to the antigen are involved.[7, 8]

That no long, *continuous* release of preformed antibodies occurs in hormone-treated man is implied by the progressive diminution in anti-streptolysin-O titers noted in two patients by McEwen and others,[16] as well as the slight decrease in serum globulin observed by the same group and by Hench et al.[17] The gradual reduction of gamma globulin to normal reported by Baehr and Soffer[18] as accompanying the hormone treatment of patients with lupus erythematosus serves as additional evidence. Likewise, Herbert and deVries[19] found that normal antibodies in the

circulation were either unaltered or somewhat reduced in concentration by the hormone.

For these various reasons, it seems unlikely that lympholytic release of preformed antibodies is the explanation for the clinical effects of ACTH and cortisone in allergic states.

The second hypothesis concerning the site of action of adrenal cortical hormones is that they alter the *rate* of antibody formation provoked by an antigenic stimulus. Conflicting evidence is to be found in the literature. White,[20] for example, could extract no antibody from the minced tissues of adrenalectomized, immunized rats but was successful with unoperated animals, particularly if they had also received ACTH. Chase, White and Dougherty[21] have described an increase in the output of globulin and of antibodies in rabbits immunized concurrently with adrenal cortical hormone administration. On the other hand, Bjørneboe, Fischel and Stoerk[14] as well as Stoerk and Solotorovsky[22] failed to confirm this enhancement of immunity in the rabbit, using more quantitative techniques. Indeed, the responses appeared to be depressed. Eisen et al[15] noted the same lack of augmentation in the rat when they used adrenal cortical extract. Germuth and Ottinger[23] found that cortisone and ACTH inhibited the development of the Arthus antibody in the rabbit. (A contrast is made between this antibody and the Schwartzman antibody by the finding of Soffer and others[24] that ACTH fails to alter the production of the latter when it is given prior to the preparatory, or initial, injection. On the other hand, the hormone can block the reaction to the secondary or provocative injection.) Our own observations, as contradictory as those cited above, appeared to depend on the time which elapsed between the preceding dose of ACTH and the antigenic stimulus, the timothy injections given at about ten hours proving effective whereas the ragweed inoculations administered at four hours were ineffectual. Although this explanation is based on a limited experience, it might reconcile some of the published results if verified.

Other theories regarding the site of action of the adrenal cortical hormones postulate an influence at or beyond the union of antibody with antigen. Carryer and Code[25] using histamine release into rabbit plasma as a gauge of antigen-antibody combination, detected no difference when cortisone was present in the test tube to which the antigen and antibody were added. According to the anaphylactic data of Leger, Leith and Rose[26] and of Friedlaender and Friedlaender[27] and Stoerk,[28]

shock in the guinea pig is not influenced by cortisone or ACTH; nor is the Arthus response to antigen blocked in this animal following its sensitization with transferred precipitins from the rabbit, as shown by Fischel[29] and Germuth.[23] From these findings it may be concluded that the antigen-antibody union, as well as the subsequent elaboration of tissue-irritating substances like histamine, and the susceptibility of nearby cells to these irritants, all remain unaltered by cortical hormones in the guinea pig.

On the other hand, the dog behaves quite differently in that anaphylaxis is diminished, albeit not prevented, if adrenal cortical extract is given prior to the challenge dose, as reported by Dragstedt, Mills and Mead.[30] In the mouse Nelson, Fox and Freeman[31] exerted a strong blocking influence against anaphylaxis by giving cortisone in large doses eighteen hours before the shocking injection. If allergic man can be considered analogous to the anaphylactic animal when he is manifesting hay fever, asthma, allergic dermatitis and overdose reactions, then he resembles the mouse and the dog more closely than he does the guinea pig. This conclusion is drawn from the observation that our patient tolerated, four hours after 10 mg. of ACTH, a larger dose of ragweed extract than could be taken by control subjects receiving no hormone. Her "challenge" response was therefore diminished in terms of the dose required to provoke it.

With reference to the influence of ACTH and cortisone on tissue susceptibility in allergic man, only a brief comment on a few patients is available in the literature,[5] to the effect that cutaneous reactivity is unaltered by ACTH. This situation is perplexing in view of the clinical effectiveness of the hormones, since the mechanism of the positive skin-test is considered identical with the antigen-antibody reaction underlying the clinical manifestations of hay fever and asthma.

Since the writing of this article, Howard, Harvey, Carey and Winkenwerder[32] have published the finding that five of their six asthmatic patients showed a reduced cutaneous reactivity to inhalant allergens under ACTH therapy and that three of their sera were titrated for sensitizing power by the serum-dilution method without any evidence of diminished output of reagins. No substantiating data accompany these statements. Leith et al[33] also state that ACTH does not alter the scratch or passive transfer results in hay fever. Furthermore, the author has confirmed this finding for two women who were deliberately given a

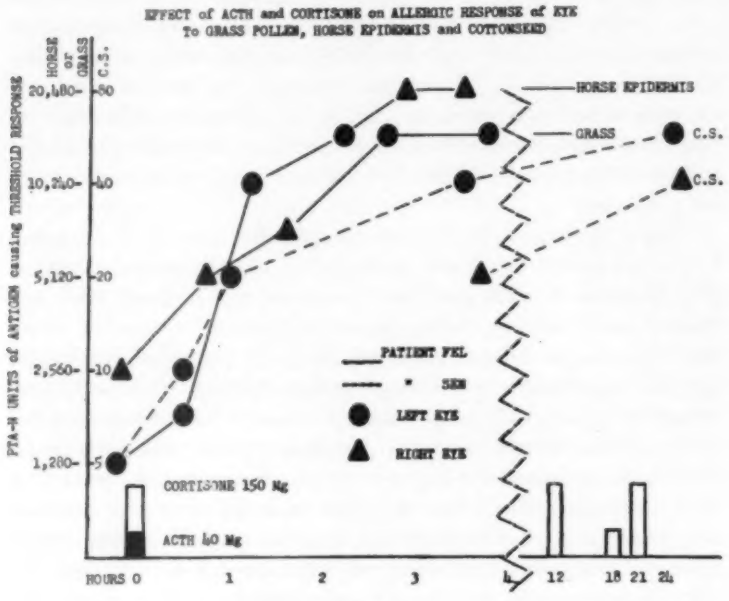

Fig. 2

large dose of ACTH or cortisone and then were periodically tested during the ensuing four hours by controlled intracutaneous and conjunctival methods. Whereas both individuals showed distinct increases in ophthalmic tolerance, no significant alteration occurred in the cutaneous allergy. The conjunctival effect commenced within ½ hour and gradually reached its maximum by 2½ or 3½ hours. The maximal ratio of change amounted to 6-fold and 16-fold, respectively, in the case of grass pollen and horse epidermal extracts which were tested in our ACTH patient (who took 40 mgs of this hormone after it had been withheld for 24 hours); and to 8-fold and 12-fold for the other, cottonseed sensitive subject who took 150 mgs of cortisone by mouth after having received none for 14 days. These results were not referable to the repeated testing of the eye, since determinations were made in the control eye at the end of each experiment and gave almost identical endpoints (Figure 2).

It recently occurred to the writer that the immunological findings described in this article, especially those surrounding specific immunization, might be importantly influenced by the *time* that had elapsed following hormone therapy. Upon making inquiry we found, however, that all tests were commenced 1½ hours after the morning injection of ACTH. Two exceptions were the studies done on June 28 and June 30, which began 6½ hours after hormone therapy. Since the conjunctival susceptibility on these dates was found to be identical with that determined for June 22 when the shorter interval and the same dose of hormone had been involved, the testing interval may be considered not to be a variable in our studies. Consequently, the increase in conjuctival resistance following pollen immunization may be attributed to antibody response rather than to technical factors. This contention is further strengthened by our more recent observation that the provocative conjunctival dose of timothy extract gradually fell during September and October, and reached a baseline of 2560 in November and in January, 1951. This behavior is characteristic of pollen immunity.

Although unconfirmed observations of Alexander et al[34] have been interpreted to indicate that all human sera contain pollen antigens during the season of pollination, this possibility does not weaken the implications of our studies albeit some of our ophthalmic and serologic studies were done during the season of grass pollination. One reason for this statement is that our hospital, located as it is in the center of a city of skyscrapers, amounts to virtually a hay fever resort where very little pollen is contacted. (Our patient was hospitalized throughout the grass season.) Another argument is that her *post*-seasonal immunologic findings were consistent with those of the season. Finally, if the patient had acquired allergens by inhalation, these would be expected to have negated rather than to have promoted the changes observed, inasmuch as the absorbed allergens could have neutralized and thereby masked the circulating and fixed tissue antibodies of either variety.[8,35]

Conclusions

1. A definite increase in tolerance, as judged by clinical improvement and lowered conjunctival susceptibility, resulted from the use of ACTH in a young woman with chronic, allergic eczema due to inhalant allergens. No shift occurred in cutaneous susceptibility.

2. No associated change in the concentration of sensitizing or of

thermostable (blocking) antibodies for the 3 etiologic allergens had occurred on or after 14 days of ACTH therapy when the serum was appraised by several techniques of passive transference.

3. Thermostable antibodies were efficiently produced when a swift intracutaneous, antigenic stimulus with timothy pollen was given in the third week 9½ hours after 10 mg. of ACTH, but no response was evoked by ragweed pollen similarly employed two weeks later when only 3¼ hours elapsed after ACTH. Hence, ACTH may have inhibited the immune response for a limited period.

4. The amount of antigen tolerated in a "challenge" dose appeared to be increased by the hormone at 4 but not at 10 hours.

5. The clinical amelioration of allergic eczema in our patient bore no detectable relation to alteration in the rate of spontaneous reagin formation, or to the "release" of preformed reagins or thermostable antibodies. The site of action of ACTH must, therefore, be at the level of union between antigen and antibody or at some point beyond this combination.

The author wishes to acknowledge gratefully the coöperation of Dr. Horace S. Baldwin and through him the Irving Berlin Fund for supplying Armour ACTH to our patient.

REFERENCES

1. Bordley, J. E., Carey, R. A., Harvey, A. M., Howard, J. E., Kattus, A. A., Newman, E. V. and Winkenwerder, W. L. Preliminary observations on the effect of adrenocorticotrophic hormone (ACTH) in allergic diseases, *Bull. John Hopk. Hosp. 85*:396-98, 1949.
2. Randolph, T. G. and Rollins, J. P. Relief of allergic diseases by ACTH therapy, *Proc. clin. ACTH Conf. 1*:479-87, 1950.
3. Samter, M. Effect of adrenocorticotrophic hormone (ACTH) on patients with allergic diseases — facts and speculations, *J. Allergy 21*:296-302, 1950.
4. Carryer, H. M., Koelsche, G. A., Prickman, L. E., Maytum, C. K., Lake, C. F., and Williams, H. L. Effect of cortisone on bronchial asthma and hay fever occurring in subjects sensitive to ragweed pollen, *J. Allergy 21*:282-87, 1950.
5. Rose, B. Studies on the effect of ACTH on eosinophilia and bronchial asthma. *Proc. clin. ACTH Conf. 1*:491-504, 1950.
6. Loveless, M. H. The conjunctival test as a guide to clinical immunity in hay fever, *Ann. Allergy 3*:333-40, 1945.
7. Loveless, M. H. Immunologic studies of pollinosis; shortening the treatment of hay fever, *J. Allergy 15*:311-31, 1944.
8. Loveless, M. H. Immunological studies of pollinosis; the presence of two antibodies related to the same pollen-antigen in the serum of treated hay fever patients, *J. Immunol. 38*:25-50, 1940.
9. Loveless, M. H. Immunological studies of pollinosis; passive sensitization of man through transfusion, *J. Immunol. 41*:15-34, 1941.
10. Loveless, M. H. *Unpublished studies.*
11. Dougherty, T. F., Chase, J. H. and White, A. Pituitary-adrenal cortical control of antibody release from lym-

phocytes; an explanation of the anamnestic response, *Proc. Soc. exp. Biol. 58:* 135-49, 1945.

12. Fischel E. E., LeMay, M. and Kabat, E. A. Effect of adrenocorticotrophic hormone and x-ray on the amount of circulating antibody, *J. Immunol. 61:*89-93, 1949.
13. DeVries, J. A. Effect of ACTH on circulating antibody levels, *J. Immunol., 65:*1-51, 1950.
14. Bjørneboe, M., Fischel, E. E. and Stoerk, H. C. Effect of cortisone and adrenocorticotrophic hormone on the concentration of circulating antibody, *J. exp. Med. 93:*37-48, 1951.
15. Eisen, H. N., Mayer, M. M., Moore, D. H., Tarr, R. and Stoerk, H. C. Failure of adrenal cortical activity to influence circulating antibodies and gamma globulin, *Proc. Soc. exp. Biol. 65:*301-06, 1947.
16. McEwen, C., Bunim, J. J., Baldwin, J. S., Kuttner, A. G., Appel, S. B. and Kaltman, A. J. Effect of cortisone and ACTH on rheumatic fever, *Bull. N. Y. Acad. Med. 26:*212-28, 1950.
17. Hench, P. S., Slocumb, C. H., Barnes, A. R., Smith, H. L., Polley, H. F. and Kendall, E. C. Effect of the adrenal cortical hormone (Compound E) on the acute phase of rheumatic fever, *Proc. Mayo Clin. 24:*277-97, 1949.
18. Baehr, G. and Soffer, L. Treatment of disseminated lupus erythematosus with cortisone and adrenocorticotropin, *Bull. N. Y. Acad. Med. 26:*229-34, 1950.
19. Herbert, P. H. and de Vries, J. A. Administration of ACTH to normal human subjects; effect on the leucocytes in the blood and on circulating antibody levels, *Endocrinology 44:*259-73, 1949.
20. White, A. Role of the adrenal cortex in immunity, *J. Allergy 21:*273-81, 1950.
21. Chase, J. H., White, A. and Dougherty, T. F. Enhancement of circulating antibody concentration by adrenal cortical hormones, *J. Immunol. 52:*101-12, 1946.
22. Stoerk, H. and Solotorovsky, M. Adrenal cortical activity in relation to lymphoid tissue and to immune bodies, *Amer. J. Path.*, in press.
23. Germuth, F. G., Jr. and Ottinger, B. Effect of 17-hydroxy-11-dehydrocorticosterone (Compound E) and of ACTH on Arthus reaction and antibody formation in the rabbit, *Proc. Soc. exp. Biol. 74:*815-23, 1950.
24. Soffer, L., Schwartzman, G., Schneierson, S. S. and Gabrilov, J. Inhibition of the Schwartzman phenomenon by adrenocorticotropic hormone (ACTH) from adenohypophysis, *Science, 111:* 303-04, 1950.
25. Carryer, H. N. and Code, C. F. Effect of cortisone upon the release of histamine during in vitro hemolytic reactions in rabbit blood, *J. Allergy 21:*310-13, 1950.
26. Leger, J., Leith, W. and Rose, B. Effect of adrenocorticotrophic hormone on anaphylaxis in the guinea pig, *Proc. Soc. exp. Biol. 69:*465-67, 1948.
27. Friedlaender, S. and Friedlaender, A. S. Effect of pituitary adrenocorticotrophic hormone (ACTH) on histamine intoxication and anaphylaxis in the guinea pig, *J. Allergy 21:*303-09, 1950.
28. Stoerk, H. C. Inhibition of tuberculin reaction by cortisone in vaccinated guinea pig, *Fed. Proc. 9:*345, 1950.
29. Fischel, E. E. Relationship of adrenal cortical activity to immune responses, *Bull. N. Y. Acad. Med. 26:*255-60, 1950.
30. Dragstedt, C. A., Mills, M. A. and Mead, F. B. Adrenal cortex extract in canine anaphylactic shock, *J. Pharmacol. 59:*359-64, 1937.
31. Nelson, C., Fox, C. and Freeman, E. Inhibitory effect of cortisone on anaphylaxis in the mouse, *Proc. Soc. exp. Biol. 75:*181-83, 1950.
32. Howard, J. E., Harvey, A. McG., Carey, R. A. and Winkenwerder, W. Effects of pituitary adrenocorticotropic hormone (ACTH) on the hypersensitive state, *J. Amer. med. Assoc. 144:*1347-49, 1950.
33. Leith, W., Graham, M. J., Burrage, W. S. Effect of ACTH on the immediate skin reaction and passive transfer test in man, *J. Allergy 22:*99-105, 1951.
34. Alexander, H. L., Johnson, M. C. and Alexander, J. H. Measurement of circulating ragweed antibodies and antigen: Correlation with symptoms and treatment, *J. Allergy 17:*340-47, 1946.
35. Eagle, H., and Loveless, M. H. Evidence for the neutralization of antigen by reagin, *Fed. Proc. 6:*426, 1947.

DIAGNOSIS OF TESTICULAR DEFICIENCIES*

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TESTICULAR deficiency is a problem which involves thousands of our men and is one which merits serious consideration by the medical profession.

The United States Bureau of the Census found that in the year 1940, 15 per cent of women forty-five to forty-nine years old, all of whom had been married, had never had a live birth. It was presumed by the Bureau that that same percentage applied to husbands. The analyses of the 1950 census will not be available for two more years but the estimates secured in 1948 indicate that there are thirty-eight and one-half million men in the United States who are, or have been, married. Therefore, more than five and one-half million of these men have had no children. There are no reliable statistics concerning voluntary and involuntary sterility in these marriages but a conservative estimate might be made that half of these married couples desired, but were unable to beget, children. Accordingly, two and a quarter million men were presumably involved with the problem of a barren marriage.

Perhaps we are now more able to reach a fair estimate of the number of men with subnormal fertility by coupling the statistics of the last census with a study recently partially completed, but not fully analyzed, by John MacLeod.[1] He has examined the semen of one thousand men whose wives have been attending the ante-natal clinic at the New York Hospital. Information was obtained concerning the duration of marriage during which no contraceptives were used before conception occurred. There can be no question that these individuals represented a highly fertile group for 20 per cent were involuntarily pregnant; 75 per cent became pregnant within six months after contraceptive precautions were abandoned; 85 per cent were pregnant within a year. Only a few reported that they had had difficulty in conceiving. This segment of the

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population therefore constitutes a group of fertile men whose semen specimens could be considered adequate for conception.

Dr. MacLeod also compiled data on one thousand individuals who were confronted with a sterility problem. The designation "infertile group" was given to these individuals although it is obvious that that is a misnomer. Included within these 1000 marriages were some individuals who, although they had not been able to cause their wives to conceive, had caused conception in previous marriages, or had been responsible for a conception ending in miscarriage. It is probable that the reason for failure to conceive was entirely or largely due to infertility of the wives of many of these men in the series. Furthermore, a follow-up study of the 1000 men included information on men who were subsequently able to produce a conception at a time after the initial semen examination was done.

A comparison of the datum gleaned from these two groups promises much for documenting our knowledge about fertility and infertility. In particular, it will furnish a basis upon which the clinical evaluation of the semen as an indicator for potential fertility may rest. Time will not permit a detailed report of Dr. MacLeod's summaries, but a few significant facts will be mentioned herewith.

Ten per cent of the "infertile" group had a complete absence of sperm in the semen. There were no cases of complete azoospermia in the fertile group. If any spermatozoa are found in the semen, it is probably incorrect to conclude that the individual is completely sterile. A reduction in the number of spermatozoa, poor motility, and increased abnormal forms permits only the assumption that the individual's capacities to reproduce are lowered. Accepting this premise as a basis for further discussion, it would seem that, if the character of the semen of these groups were without any significant difference, the conclusion might be justified that the quality of the semen was not a representative factor in the fertility of one group as compared to the infertility of the other. Furthermore, if definite variations in the semen between these two groups were found, such a disparity would be meaningful for the groups were sufficiently large to have statistical value for comparison. Each category of the semen analysis was compared individually and then collectively.

No significant dissimilarity was found between the fertile and "infertile" group as far as the volume of the ejaculates was concerned.

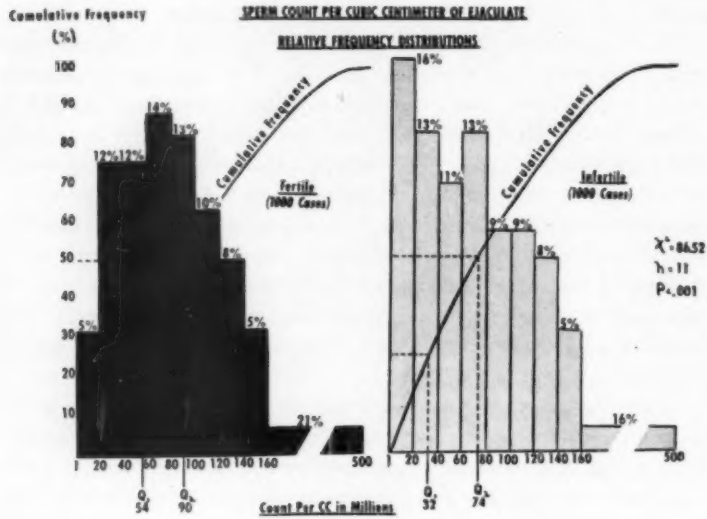

Fig 1.

As illustrated in the above graph, there is a significant contrast between the two groups as far as the content or numbers of spermatozoa were concerned. The azoospermic cases were entirely eliminated from the following calculations (Fig. 1).

This occurred rather sharply at the twenty million spermatozoa per cubic centimeter level. It will be seen that one-fourth of the "infertile" group had counts under thirty-two million spermatozoa per cubic centimeter, whereas 25 per cent of the fertile men had counts under sixty million. Table I illustrates this variation between the two groups in a perhaps more striking manner. The one thousand fertile and "infertile" cases were sub-divided into categories according to their counts per cubic centimeter. Each category thereby represented individuals having cell counts per cubic centimeter in multiples of twenty million. For instance, the first group is 0 to 20,000,000 cells per cubic centimeter, the second are those cases who had cell counts within the limits of 20,000,000 to 40,000,000 while the third is 40,000,000 to 60,000,000, etc. If the

TABLE I

	Group I (2000 Cases)			Group II (925 Cases)			Group III (925 Cases)		
	A. Fertile Marriage (1000 Cases)			A. Men in infertile marriage with history of conception(s) prior to semen exam (241 Cases)			A. Men in infertile marriage with conception(s) prior to *or* after semen exam (319 Cases)		
	B. Infertile Marriage (1000 Cases)			B. Men in infertile marriage with history of no conception prior to semen exam (684 Cases)			B. Men in infertile marriage with no conception prior to or after semen exam (606 Cases)		
Count per Cubic Centimeter in Millions	*No. of Cases in Count Class*	*Proportion Contributed by A*	*Difference from 50.0%*	*No. of Cases in Count Class*	*Proportion Contributed by A*	*Difference from 26.1%*	*No. of Cases in Count Class*	*Proportion Contributed by A*	*Difference from 34.5%*
All Cases	2000	50.0%	——	925	26.1%	——	925	34.5%	——
Under 20	211	21.8%	Signif.	152	13.2%	Signif.	152	19.1%	Signif.
20-39	248	47.1%	Not Sig.	118	26.3%	Not Sig.	118	37.3%	Not Sig.
40-59	227	52.7%	Not Sig.	104	26.0%	Not Sig	104	30.8%	Not Sig.
60-79	271	52.4%	Not Sig.	120	21.7%	Not Sig.	120	35.0%	Not Sig.
80-99	220	59.1%	Signif.	81	34.6%	Not Sig.	81	43.2%	Not Sig.
100-119	191	49.7%	Not sig.	83	37.3%	Mod. Sig.	83	44.6%	Mod. Sig.
120-139	157	52.2%	Not Sig.	69	20.3%	Not Sig.	69	30.4%	Not Sig.
140-159	96	52.1%	Not Sig.	45	28.9%	Not Sig.	45	37.8%	Not Sig.
160-Over	369	57.7%	Signif.	153	33.3%	Mod. Sig.	153	40.5%	Not Sig.

Significant—probability less than .01
Mod. Signif.—probability between .01 and .05
Not Signif.—probability greater than .05

count per cubic centimeter were not a discriminating factor in fertility, one would expect the number of cases falling in each count classification to be equal to the proportions contributed. Fifty per cent were contributed by the fertile group and 50 per cent were contributed by the "infertile" group. Consequently the laws of chance require that equal numbers of men would be found in all categories unless the count per cubic centimeter were influencing the chance of conception. The chart shows that the fertile marriage group contributed only 22 per cent to the cases under 20,000,000 cells per cubic centimeter. As one proceeds toward the higher counts, an equalization is arrived at and each contributes approximately 50 per cent. Accordingly, this information suggests that, when the cell count per cubic centimeter is low, below twenty million cells, the chances of conception are decreased.

A study of the motility of spermatozoa shows, likewise, even a more significant discrepancy between the two groups. The statistical analysis of the information relative to motility is not yet processed. It is revealed, however, that only 1 per cent of the fertile men had counts per cubic centimeter less than twenty million linked with poor motility whereas 8 per cent of the "infertile" men had such a combination.

Let us return now to the statistics provided by the last census report. For reasons previously cited the true incidence of involuntary sterility remains unknown. A liberal estimate might be that half the married couples do not desire children and are using contraceptives. Ironically enough many of these are sterile. We might assume from Dr. MacLeod's datum that there are one-half million and more married men in the United States who have no spermatozoa in the semen. Furthermore, it can be inferred that there are at least between three and four million married men in the United States with sperm counts below twenty million per cubic centimeter. With due allowances for errors in these estimates, it remains obvious that infertility constitutes one of the larger medical problems in the United States today.

Medical knowledge is made up of two types of reasoning. One is theory – an example of which is to be found in the discussion thus far. The second is factual knowledge. This allows no area for dispute or controversy because the information is established. In a young, or new branch of science, the theoretical information may outbalance the facts. Such is true in the study of human reproduction.

Testicular biopsy has provided, however, a body of factual knowl-

edge as related to men with impaired fertility. There remains much to be desired to be known about the causes of these cytological changes found in the testes yet it would seem important to discuss the patterns of testicular dyspermatogenesis for these abnormalities affect thousands of American men. It is worth while to reiterate that many of these changes occur in otherwise healthy, normal men, possessing all the complements of complete masculinity and having what appears to be normal genitalia.

Testicular biopsy is a valuable clinical aid in differentiating whether an azoospermia is due to a blockage of the vas or to a complete or partial failure of spermatogenesis. Considerable histological material has also been obtained from men with a reduced number of spermatozoa in their ejaculate, particularly those individuals having cell counts less than twenty million cells per cubic centimeter. Nelson[2] aptly commented that "a testicular biopsy serves as a role in the diagnosis of the defects of the gonadal function in a manner even superior to endometrial biopsy in the female. The latter reflects the character of ovarian endocrine function without revealing defects in gametogenesis, whereas the testicular biopsy furnishes an exact observation of the male sex cell." In deficient spermatogenesis, there are five fundamental types of spermatic defects. These have been designated:

1) Germinal aplasia; 2) Spermatogenic arrest; 3) Generalized peritubular fibrosis; 4) Incomplete maturation and disturbed spermatogenesis; 5) Complete fibrosis.

One individual may show many varieties of these disturbances by a single biopsy secured from the testes, or he may show only one. Before providing examples of each type, it is well to review the characteristics of a normal seminiferous tubule.

Normal Seminiferous Tubule

The peritubular membrane is represented by a line separating the interstitial cells from the spermatogenic cells. All the blood vessels are found in the interstitial areas and it is presumed that the nutritive elements must pass through the membrane to reach the germinal cell. Likewise, the waste products of metabolism must pass out of the tubules by perfusion through the peritubular membrane. The oval or fusiform cells of Sertoli are located just above the spermatogonia insinuating radially into the lumen of the tubules. Sertoli cells have the only oval nuclei found

in the cells of the germinal epithelium. Primary spermatocytes have the largest nuclei around a chromatin network which is clearly visible. The primary spermatocytes are larger than the secondary spermatocytes. The spermatids are recognized by dark nuclei near the border of the lumen. One often sees spermatozoa embedded in the cytoplasm of the Sertoli cells which have been considered to be a nutrition or trophic cell.

Germinal Aplasia: The tubules are usually uniform in size. The striking feature is a complete lack of germ cells. The only epithelial structures may be the Sertoli cells. Occasionally a few tubules may show a sprinkling of germ cells but mitosis does not go beyond the spermatogonia or primary spermatocyte stage.

Spermatogenic Arrest: The tubules are usually of normal size and many spermatogonia, primary spermatocytes and Sertoli cells are seen. An arrest of mitosis may occur at any stage but is most commonly seen at the primary or secondary spermatocyte level. In any event, the results are the same. Few if any mature spermatozoa are produced and there will be abundance of debris and exfoliated cells in the lumen of the testicular tubule.

Generalized Peritubular Fibrosis: The diameter of the seminiferous tubule varies inversely to the degree of fibrosis. Mitosis likewise is directly proportionate to the amount of fibrosis about the tubule. The spermatogenesis may be complete with slight fibrosis but invariably reduced if heavy. All intratubular cellular structures may be lost with extreme fibrosis.

Incomplete Maturation and Disturbed Spermatogenesis: Tubules connected with this type of dyspermatogenesis are found in men who have counts below average and/or a large number of abnormally formed spermatozoa in their ejaculate. Peritubular fibrosis may be absent or present in varying degrees, commonly there is a sloughing of immature cells into the central lumen of the tubule. A significant histological change is atypical mitosis, particularly at the reduction stage of the division. Distortion of the nuclear material in the cell can only be appreciated with proper staining. Aberrant mitosis and abnormal chromosomal behavior are correlated with atypical forms of spermatozoa in the ejaculate (Engle[3]).

Complete Fibrosis of all tubules is usually associated with small testes. Interstitial cells are correspondingly prominent because of the disappearance of the tubules themselves.

TABLE II

Semen Analysis	*Testis Biopsy*
1. Normal sample	
2. Azoospermia	a. With demonstrable occlusion 1. normal tubules 2. disturbed spermatogenesis
	b. Without demonstrable occlusion 1. normal tubules 2. progressive tubular fibrosis 3. Germinal aplasia 4. Spermatogenic arrest (to spermatocyte I)
3. Oligospermia	a. With high frequency of abnormal spermatozoa 1. incomplete maturation 2. progressive tubular fibrosis
	b. Inflammation and infection

Engle[4] has formulated a classification which is presented herewith, allowing comparison of these cells with the semen analysis (Table II).

Thus far, we have presented two facts: 1) a larger percentage of husbands who have no issue have poorer semen than those with children; 2) certain testicular patterns have been classified and are definitely correlated with infertility. Lack of specific knowledge now forces us to step from the barricades of facts to the luxury of theories, since definite knowledge is not at hand to explain adequately all the changes in the testes of men with lowered fertility. It is possible and probable that the same factors or forces which produce the testicular patterns heretofore described and related to azoospermia or marked oligospermia likewise may account for less severe depressions of the quality of the semen. If such is true the difference between the moderately subnormal seminal specimen and the one who has no sperm, yet has certain spermatogenic activity, may be only a matter of degree.

Time will not permit a complete exposition of all the possible factors that might account for dysfunction of the testes, but a few are selected for discussion because they may be reversible and thereby imply the possibility of correction or control.

Treatment of the infertile male has not been satisfactory and any leads toward better therapy deserve the attention of those who seek to

benefit these patients. Therefore, we shall not concern ourselves with the possibility of genetic faults and embryologic disorders in the germ cells which might be responsible for some of these testicular abnormalities. They would be refractory to any attempts of man to change. We shall eliminate also irrecoverable atrophy such as follows mumps orchitis. Neither is it germane to relate how surgical cure of obstructive azoospermia is sometimes accomplished. We shall confine our attention to four types of agents which in theory may have exerted their damage during pre-pubital or during post-pubital life. They are: 1) nutrition, 2) deficiency diseases, 3) metabolic disturbances, and 4) the endocrines.

Nutrition: Proper nutrition of the testes is essential to normal function. Laboratory experiments have shown that a deficiency of vitamins A and E cause profound testicular damage without affecting the interstitial cells. Species variation to avitaminosis is illustrated by the fact that vitamin B deficiency can produce testicular changes in birds but not in mammals. It is unlikely that testicular changes described hitherto are due only to a faulty intake of the various vitamins. Deleterious defects can best be explained by improper utilization of vitamins on an individual basis, for there is a recognized distinction between minimal and optimal requirements. Thyroid substance and vitamins have been used in an attempt to improve the quality of subnormal semen specimens. It is exceedingly difficult to evaluate the effectiveness of these materials, although some individuals have exhibited an improvement in the semen coincidental to, or as a result of this type of therapy.

Deficiency Diseases: The regressive changes in the testes can conceivably be due to a deficiency of materials other than vitamins. It is known that certain amino acids are a requisite for normal testicular function. The requirement of the testes for minerals remains unknown, and yet it is not beyond the bounds of theoretical possibilities that minerals peculiar to the needs of the testes may account for a reduced output of sperm. Analogy may be found in the bone marrow in its need for iron, and in the thyroid, for iodine. Such a specific mineral or substance remains unknown, but the therapeutic implications are obvious if such a specialized tissue need is ever shown to be a peculiarity of the testes.

Metabolism: A growing body of evidence indicates that the liver plays a vital role in complex body relationships between the enzymes and the endocrines. Glass[5] and Biskind[6] in particular have stressed the

importance of the liver to testicular maintenance. The inactivation of the estrogens is dependent upon normal liver function. Estrogens which escape oxidation may alter the pituitary responses and produce a hormonal imbalance. Furthermore, spermatogenesis itself might be interrupted by an excess of circulating estrogens which were not inactivated by the liver. There is reason to believe that a normal functioning liver is essential to a normal functioning testis.

Endocrines: The hypothalamus-pituitary-adrenotestis relationship has been extensively studied and the literature is vast as well as confusing. There are six or more hormones elaborated by the pituitary of which four may bear on the subject of testicular function.

Follicular stimulating hormone (F.S.H.), lutinizing hormone (L.H.), and lactogenic hormone (L.T.H.) are collectively known as the gonadotropic hormones. FSH is directly concerned with the testicular tubules, for it is thought to stimulate both the spermatogenic and Sertoli cells. LH controls the secretion of the testicular androgen produced by the interstitial cells of Leydig. The role of the lactogenic hormone is less clearly defined in the male, but it may be coupled with LH and have an influence upon the Leydig cells. The fourth pituitary hormone, the adrenocorticotropic hormone (ACTH), stimulates the reticular cells of the adrenal cortex to produce the twenty-eight or more steroid hormones. Eleven of these compounds have biologic activity. It is with the three androgenic steroids, and with esterone, that we are concerned, for the adrenals contribute more androgenic activity to the body than to the testes. The androgens are able to preserve regressive changes in the secondary sexual characteristics consequent to castration. Testosterone usually prevents atrophy of the germinal epithelium in hypophysectomized animals. It can cause growth of the accessory male genitalia. Its exact role in the maintenance of spermatogenesis in the human is not entirely clear. There has been a recrudescence of interest in the Sertoli cell in recent years, and a controversy now exists concerning the ability of the Sertoli cell to produce a hormone under the influence of FSH. Some evidence is at hand to suggest that this hormone is an estrogen. Others believe that the hormone possesses a distinct action of its own and have designated the product as the "X" hormone and also "inhibin." Viewed in the latter light it is a non-androgenic substance which has the power to retard or inhibit the production of F.S.H. by the pituitary. Likewise, the theory has been advanced that it stimulates LH production

and by itself supports spermatogenesis. The proponents of the "singular" testicular theory, however, point out that the "X" hormone has not been isolated and the FSH secretion will be depressed by sufficiently large amounts of testosterone. Controversial as many of the endocrine relationships now are, the fact remains that the fate and the function of the testes are at the mercy of the endocrines of which they are a part.

Utilization of the knowledge of this complex organization has led to many types of therapeutic plans. The results from administration of available gonadotropins, however, have been disappointing. The failure to elicit definite and consistent clinical improvement is attributed to antihormone response, species specificity, and lack of precise tests to indicate their use. Recently much attention has been given to Heller's observations relative to the stimulating action of testosterone propionate.[7] He reported that twenty-five milligrams of testosterone propionate a day for ninety days caused marked atrophy of germinal epithelium. This was followed by a reconstruction that, within one and a half years, was superior to that before any treatment was given. The effects implicated the activity of "inhibin" on the pituitary. The real worth of his observations await more confirmation by himself and other investigators.

The coupling of facts and theories furnishes the material by which more factual knowledge is developed. Thousands of American men may be benefited by the discovery of even one more etiological influence causing the abnormalities of the germinal tissue. Once the cause is firmly identified, the means of correcting the defect comes much closer to realization. The present development of our knowledge in this field permits justified hope that much may be anticipated in the future.

REFERENCES

1. MacLeod, J. Male factor in fertility and infertility, *Fertility & Sterility 1*:347-61, 1950.
2. Nelson, W. O. Testicular morphology in eunuchoidal and infertile men. *Fertility & Sterility 1*:477-88, 1950.
3. Engle, E. T. Atypical cytology in testes biopsies, *J. Urol. 62*:694-700, 1949.
4. Engle, E. T. Testis biopsy in infertility, *J. Urol. 57*:789-99, 1947.
5. Glass, S. J. Rational approach to the problems in functional sterility, *Ann. west. Med. Surg. 4*:599-602, 1950.
6. Biskind, G. R. Experimental demonstration of inactivation of certain sex steroid and estrogens in vivo, in *Medicosurgical tributes to Harold Brun*, Berkeley, University of California Press, 1942, pp. 41-58.
7. Heller, C. G. et al. Improvement in spermatogenesis following depression of human testis with testosterone, *Fertility & Sterility 1*:415-21, 1950.

THE HUMANITY OF SIR THOMAS BROWNE

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IN an address on Sir Thomas Browne delivered at Guy's Hospital in London forty-six years ago, Sir William Osler appealed to "the compassionate feeling with which the bibliomaniac is regarded by his saner colleagues." Frankly confessing an unbounded enthusiasm for my subject, I must also solicit the kindly tolerance which the medical profession has always shown towards human aberrations—of which it daily sees so many. I recall vividly the occasion when a distinguished member of this group, Dr. Eli Moschcowitz, permitted me—a perfect stranger—to examine some of his precious copies of Sir Thomas Browne, recognizing instantly and sympathetically one whose passion for old books was past redemption. Perhaps it is presumptuous of a layman lacking Osler's extensive learning to speak to physicians of a physician, but since many medical persons have written on literary subjects, a student of literature may venture to discuss a physician who was very literary indeed.

The many rare volumes in the Osler collection, like those in the famous library of this Academy, are constant reminders that the history of medicine is a history of medical men—their failures and their achievements, their follies and their insights, their ignorance and their wisdom. Osler well knew that in the art of healing the physician deals with humanity, to whom nothing is alien, where the boundaries between mind and matter are obscure. His interest in Sir Thomas Browne went deeper than mere delight in the "quaintness" which captivated the nineteenth century critics. In his library the Browne collection is given an honored place beside the niche containing, in the words of Dr. William Francis, "Osler's adjacent ashes." For in Thomas Browne, Osler found a good and true friend with a "deep human interest in human beings." *Religio Medici*, he stated quite simply, "is the most precious book in my library."

When we turn the pages of this little volume, we recall that it was published in the fateful year 1642, when the clash of arms at Edgehill sounded the beginning of open war between Parliament and Crown. The uncertainties of our times may seem no more ominous to us than those violent struggles seemed to peace-loving Englishmen three hundred years ago. Into a tumultuous atmosphere came this doctor's confession of faith, quietly enough, without fanfare, in a drab little octavo that is now prized by collectors. Readers discovered, as we discover today, that here was a lively personality who believed in God, in his fellow-men, and in himself. The author's name did not appear on the title page, for the book had been published surreptitiously. But his profession, and the paradox inherent in the title, attracted immediate attention. In those days many supposed that a physician, who presumed to tamper with God's handiwork, must somehow be in league with the powers of darkness.

The story of *Religio Medici*'s meteoric fame is well known. The widespread interest it first aroused grew into a storm of controversy. The energetic Sir Kenelm Digby sat up all night reading it, and wrote his *Observations*, which were soon published and prompted Browne to come out with "a true and full copy of that which was most imperfectly and surreptitiously printed before under the name of *Religio Medici*." The book became a true best-seller. It was translated into several languages, excited admiration on the Continent, and gave rise to a host of imitations, so that today Mr. Geoffrey Keynes can enumerate eighty-five religios of all sorts—from *Religio Laici* to *Religio Obstetrici*. Browne did not rest on his early fame as the celebrated author of a popular essay; he continued to write, and in his longest book, *Enquiries into Vulgar Errors*, attempted a large-scale examination of popular beliefs. This work was a forerunner of the new investigations which were to be carried on by the Royal Society. Other minor writings appeared, including that masterpiece of English prose, *Urn Burial*, containing reflections on life, death, and immortality in some of the loveliest and most solemn passages in the English language.

It used to be the fashion to characterize Sir Thomas Browne as a dreamy antiquarian, withdrawn from the busy world and oblivious to what was taking place around him. However, his correspondence shows that he was nothing of the sort. It is full of comments on local doings and events in England and abroad. But even if this correspondence had

not survived, we should know that Browne was no recluse, because for nearly half a century he carried on an extensive medical practice as a general practitioner in the city of Norwich. Dr. Browne was probably more familiar with the human concerns and daily activities of his fellow men than many of his more worldly contemporaries. Moreover, he was in his own time eminent in his profession—"much resorted to by his patients for his admirable skill in Physick," as an Oxford biographer put it. He was made a fellow of the Royal College of Physicians, of which his son Edward later become president.

Browne had received his medical training at the most advanced schools on the Continent—Montpellier, Padua, and Leyden, and was always keenly interested in anything new. To be sure there is a certain bookishness about his medical comments, as there is about much in seventeenth century culture, but he was at least as advanced as many of his contemporaries, and more alert and ready to experiment than most. Towards Harvey he was enthusiastic, and preferred his account of the circulation of the blood to the discovery of Columbus. He nevertheless poked fun at Harvey for having written excellently on generation, while having no offspring of his own. Sydenham's book, *De Febre Putrida*, he pronounced "well writ." Famous names appear in Browne's correspondence—Glisson, Ent, Lower, Highmore, Charleton, and Mayow. In 1667 he asked his son to try at Calais to "get a box of the Jesuits powder at easie rate & bring it back in the bark, not in powder." In a reply to an inquiry about the efficacy of quinine he sensibly stated that he had seen no bad effects from its use, though it "doth not so much good as I could wish." He scoffed at physicians who diagnose all ailments by examining urine, as if it were "the Oracle of life, the great determinator of Virginity, Conception, Fertility, and the inscrutable infirmaties of the whole Body." He was doubtful about bloodletting, and surmised that it must be less valuable than purging, "since in the Generall purging cures more diseases," and since, "there are so few hints for bleeding from any naturall attempt" in animals. Of the use of antimony he was sceptical, and proposed that "an exact and critical trial" be demanded by the public.

But more interesting to me—and safer ground—is the continuing thoughtful interest Browne shows in his patients. His letters to his son Edward practicing in London reveal him as a wise practitioner who knew something of the rudiments of psychotherapy, combined patience

with shrewd common sense, and had genuine concern for those in his care. For one patient he described the treatment successfully given another, with the cautious reservation: "Butt there is a great disparity in your constitutions and purging medicine hee used will not bee proper for you."

He writes Edward of a Mrs. Suckling, who is complaining of a "vehement payne in the legge" and is coming to London to consult a surgeon about an ulcer in her nose. "I had no reason to conjecture," he explains, that there was anything suggesting syphilis, "shee beeing a vertuous good woeman." "Shee is likely to bee in great perplexity if you should positively tell her. . . ." "Pray have a speciall care of her for shee is a very good person."

Also to consult Edward is "Mr. Alderman Wisse": "a meticulous doubting man of a good nature . . . seldome without thoughts to perplex himself & making his life the more uncomfortable . . . I am fayne to compose him sometimes by good counsell and rationall argument; the truth is hee is a very honest inoffensive person & his owne foe most."

Of a Mr. Hasset, Sir Thomas cautions: "hee intendeth to marry, and hath settled affection upon a good gentlewoeman. . . . I would have you to vewe the penis diligently. . . . for hee is very Jealous and apt to bee meticulous, and is hypochondricall."

"Mr. Payne of St. Gyles" is to come to London. "You must have good patience, for hee abounds in questions & doubts, & is soone discouraged & apt to laye hold of any words & to argue agaynst himself or any remedies."

We hear also of physicians' own troubles. "Extraordinarie sickly seasons woorie physitions, and robbeth them of their health as well as their quiet." "Therefore," he advises Edward, "have a great care of your health. . . . which may bee by Temperance and sobrietie and a good competence of sleepe. Take heed that Tobacco gayne not to much upon you." In his later years Sir Thomas himself felt increasingly the strain of keeping up his practice and confessed: "I am fayne to keep my self warme by a fire side this cold wether."

Of Browne's various writings that which most strikingly blends medical and human interest is an essay describing the death of a young man suffering from phthisis. Entitled *A Letter to A Friend*, it was printed in folio from among Browne's posthumous papers, and is now an excessively rare book. Recently the young man has been identified

as Robert Loveday, a poet who had been in correspondence with Sir Thomas. The remarkable thing about this little tract, which Walter Pater preferred above all Browne's other works, is that its raw material was an actual case from the physician's notebook. Dr. Browne saw that death was inevitable and so informed the patient's relatives. Noticing that the stricken man had once suffered from rickets, Browne pauses to remark that it would be worth knowing whether the children of English planters abroad suffered from the same disease. He comments on the patient's beard and thick hair, then recalls observing, when a student at Montpellier, "that Endemial Distemper of little children in Languedock, called the Morgellons"—a skin ailment described obscurely in a number of medical books of that time. He states that he was not surprised to find that "two Lobes of his Lungs adhered unto his side; for the like I have often found in Bodies of no suspected Consumptions or difficulty of Respiration. And the same more often happeneth in Men than other Animals: and some think in Women than in Men."

But all this and other acute observations combine, in this "elfin essay" as Pater called it, with fascinating digressions. Every impression, every symptom of death leads to an imaginative speculation. The end of physical existence—the final dissolution—has a powerful effect on his imagination. He muses over the patient's dreams. The gradual change in the young man's countenance leads to queries about physiognomy. The hour of death calls forth a digression on the significance of dying on one's own birthday—which is exactly what happened to Sir Thomas himself. The thought of "the mighty Nations of the Dead" evokes rich and poetic phrases: "He left this World not very many days past, yet every hour you know largely addeth unto that dark Society."

The personality of Sir Thomas Browne can be discovered not only in his medical observations but also in his miscellaneous comments, which display a restless, wide-ranging curiosity. These notes, probably kept late at night when the last patient had been dismissed, may be read in his nervous and distinctive handwriting in the British Museum, where Browne's papers were deposited by another distinguished physician, naturalist, and collector, Sir Hans Sloane. Here is a sample:

> To find out a body that will precipitate salt in a solution of water. . . . Wheat sprouteth up within a fortnight or 3 weeks after it bee sowed. . . . Trie

therefore whether sowne in April it will not come to perfection that yeare. This performed—wheat sowne in April came up well, thick, spindled late, eared late. . . . To manifest how lasting the seminall principles of bodyes are, how long they will lye uncorrupted in the earth. . . . Litle red wormes and lesse than threads are found in great numbers in diches & muddy places where the water is almost forsaken. . . . To observe whether in fearfull animals as the hare, doe, &c. the crystallyne humor of the eye bee more turgide whereby objects seeme greater unto them. . . . 3 grains of opium workes strongly upon a dogge. Observe howe much will take place with an horse, wch subsisteth with litle sleepe. . . . 4 unto a crowe without visible effect. . . . 6 & 8 unto dogges making them dull, not profoundly to sleepe. . . . 2 grains given a pickerell above a quarter long dyed in twelve howers, floted not; another whoe had nothing given survived.

Dr. Johnson, who was a great admirer of Sir Thomas, once asserted that any sort of knowledge is worth acquiring, and Browne himself certainly seems to have thought so. His old friend Whitefoot declared that he seemed to have been ordained by Divine Providence to be "Surveyor-General of the whole terrestrial Orb." The names of most of Browne's leading contemporaries in science appear in his writings. He read eagerly the publications of Harvey, Descartes, Hooke, and Boyle. In early middle age, fourteen years before the Royal Society was organized, he suggested the possibility of "cooperating advancers" of learning, and in his seventies advised his son Edward to notice Leeuwenhoek's observations of spermatozoa.

Browne inclined toward the biological sciences, especially in his later years, and he was profoundly aware of the central problem which has challenged the best minds of every age – the nature of man. Today new explorations into the complexities of the nervous system and the insights of modern psychology have increased our knowledge but have deepened our perplexity. In Browne's time men puzzled over the question of the inorganic soul. In the human skull "there is not any thing of moment more," he observed, "than I can discover in the crany of a beast . . . thus we are men, and we know not how." Yet he never permitted his "haggard and unreclaimed reason" to lure him down the path to utter materialism. The uncompromising reduction of all things to naturalistic concepts, so appealing to a Hobbes, a Huxley, or a Freud, seemed to Browne neither valid nor adequate as an account of man and the universe. What he could discern with his own eyes turned his "Philosophy into Divinity." "There is," he wrote, "in these works of nature, which seem to puzzle reason, something Divine, and hath more in it than the eye of a common spectator doth discover." Nor was this

simply the wish-fulfillment of a naive theist. He had pondered deeply the question of generation, and had spent hours watching duckweed in water in the hope of fathoming the mysterious process of growth. The egg – the seed – seemed to him, as to us, dramatic mysteries, suggestive of the unknown force that seems to lie behind all living things. To observe the process of generation he said "were a sight beyond all." It is a "great work whose wonders are only second unto those of the Creation and a close apprehension of the one, might perhaps afford a glimmering light, and crepusculous glance of the other."

Although Browne did not live to witness the complete triumph of the principles of Newtonian physics, which were to dominate man's thinking for two centuries, he could have accepted them readily because of their suggestion of a majestic universal order. Like his contemporaries, he conceived of the visible world as a static affair. Yet he was extraordinarily conscious of the relativity of time, and was impressed by the paradox that man, with his pitifully short span of years, is yet aware of the eternal and infinite. Browne was irresistibly drawn to thoughts of antiquity. The grand sweep of the centuries, the majestic flow of "time that grows old in itself" and "makes all that is past a moment" haunted his meditations. Thoughts of ancient times stirred his imagination. Homer and Plato were table companions, Alexander and Caesar next-door neighbors, and the first drama of mankind in Paradise was enacted not so long ago. But he saw it all as if enveloped in a veil which the mind of man cannot pierce.

Browne amused himself with predictions and in some doggerel verses actually foretold things to come: the end of the slave trade, the rise of America to world dominance, trade in the Pacific, American armies in Europe, and even the subjugation of China by "a new drove of Tartars." In another place he proposed the digging of the Panama Canal. But he himself did not take his prophecies seriously, and once observed: "if you have a mind to laugh at a man, or disparage the judgment of any one, sett him a talking of things to come . . . wherein men seem to talk butt as babes would do in the womb of their mother, of the things of the world which they are entering into." Sir Thomas usually preferred to glance back down the stream of time, and expected revelation of the future only in dark hints. Some, Browne remarked in *A Letter to a Friend*, might wish to have lived in past ages, but "the uncertainty of future times hath tempted few to make a part in Ages

to come. And surely, he that hath . . . rightly calculated the degenerate state of this Age, is not likely to envy those that shall live in the next, much less three or four hundred years hence."

We who live almost exactly three hundred years later may wonder whether, despite the vast increases in our knowledge, we are living better than our seventeenth-century ancestors. Certainly in human conduct and understanding we have not advanced beyond the sane and balanced outlook of Sir Thomas Browne, who at the end of his essay leaves medical and psychological considerations to affirm that length of life is less important than the values by which life is lived. The dying young man had "already fulfilled the prime and longest Intention of his Being: and one day lived after the perfect Rule of Piety, is to be preferred before sinning Immortality."

Sir Thomas Browne had a kind of double vision. He saw the world as the handiwork of an all-powerful creator challenging man to explore its secrets, and at the same time as a hieroglyph concealing its deepest meaning. To lay open the fabric of the human body, to explore the earth, or to study the stars is no impiety but rather a means of honoring God's wisdom. But man's powers are limited. One may glimpse, but not grasp, the absolute:

> "In vayne wee seeke to satisfy our soules in narrow theories & close apprehensions of the divine essence. . . . The divine revelation in such poynts being not framed unto intellectualls of earth."

To the early Christian, intent on the world to come, this life is but a corridor through which man walks to his death. To many others this life is all-important. Sir Thomas Browne resolved the two points of view. Though he pronounced man "that great and true Amphibium" living "in divided and distinguished worlds," he found no conflict between the two worlds. His belief in a higher being served not to lessen his concern for humanity but to strengthen it. Though he could not truly understand man's nature, he did not conclude that it has no meaning. The fact of his own existence and the existence of his fellow-men seemed an overwhelming reason for living this life to its highest degree of fulfilment. He was moved to affirm rather than to deny. As a physician, whose daily concern was life and death, he was keenly aware of the helplessness and the dignity of man. The reconciling principle, he believed, is charity. *Religio Medici*, his earliest and most eloquent expression of his convictions, stands as one of the first great pleas for

tolerance. At a time when fanatic partisanship and unyielding prejudice seemed to dominate men's thinking, he confessed:

> I feel not in myself those common Antipathies that I can discover in others: those National repugnances do not touch me.

When harsh reformers were condemning all who opposed them, he calmly observed:

> No man can justly censure another, because indeed no man Truly knows another. . . . No man can judge another because no man knows himself.

In an age when doctors were often more concerned with their patients' fees than with their welfare, he entreated:

> Let me be sick myself, if sometimes the malady of my patient be not a disease unto me; I desire rather to cure his infirmities than my own necessities.

A note in his commonplace books contains his private reminder: "To pray dayly and particularly for sick patients. . . . Upon sight of beautiful persons to blesse god in his creatures."

Sir Thomas Browne managed his own daily responsibilities with good sense and practicality, yet felt God's nearness to every act of daily life and believed that "surely there is a piece of Divinity in us." To the logical minds of the eighteenth century, such a man did not appeal. They dropped into cold, rationalistic pronouncements on the subject of life and death. The breathless hush which had fallen on the author of *Urn Burial* was broken by the clamor of reasoning theologians. Under the searching glare of their analytical minds the delicate hues of Browne's imagination were indiscernible.

But in the next century, and in our own, the warm humanity of Sir Thomas Browne has been rediscovered. Long before Osler, a spirit kindred to Browne's, Charles Lamb, responded to the rare humor, keen intellect, and warm charity in Browne's writings. A famous conversation has been recorded, in which someone asked Lamb what men in history he would most wish to have seen:

> On the question being started, Ayrton said, "I suppose the two first persons you would choose to see would be the two greatest names in English literature, Sir Isaac Newton and Mr. Locke?" . . . Everyone burst out laughing at the expression of Lamb's face, in which impatience was restrained by courtesy. "Yes, the greatest names," he stammered out hastily, "but they were not persons—not persons." . . . Lamb then named Sir Thomas Browne and Fulke Greville, the friend of Sir Philip Sidney, as the two worthies he should feel the greatest pleasure to encounter on the floor of his apartment in their nightgown and slippers, and to exchange friendly greetings with them.

Browne was indeed a person, and would have been amused at Lamb's desire to exchange greetings with him. He once wrote in his notebooks:

> "I cannot fancy unto myself a more acceptable representation or state of things then if I could see all my best freinds, and worthy acquaintance of fortie yeares last past, upon the stage of the world at one time."

Here, then, is our humane physician: scientist, antiquarian, and author, deeply religious and wisely tolerant – eminently a man of good will. Though his fame is rather in the annals of literature than the history of medicine, the medical profession may own him proudly. In the most difficult of all tasks – that of living one's life with courage, kindness, and wisdom – he conspicuously succeeded. But his service to mankind has transcended his own lifetime. It has continued through three centuries in the pages of *Religio Medici*, where many generations of readers – laymen and physicians alike – have discovered the humanity of Sir Thomas Browne.

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Aguilar, O. P. & Queirel, J. Broncon-eumonectasias congénitas. Buenos Aires, [Vazquez], 1948, 206 p.

Aguilar, O. P.; Sirlin, G. & Schneier, M. Tuberculosis pulmonar hematogena. [Buenos Aires], El Ateneo, 1948, 208 p.

American Cancer Society. A cancer source book for nurses. New York, Cancer Society, [1950], 119 p.

Association of Official Agricultural Chemists. Official methods of analysis. 7.ed. Wash., The Association, 1950, 910 p.

Axhausen, G. Die allgemeine Chirurgie in der Zahn-, Mund- und Kieferheilkunde. 4.Aufl. München, Hauser, 1949, 461 p.

Bawden, F. C. Plant viruses and virus diseases. 3.ed. Waltham, Mass., Chronica Botanica Co., 1950, 335 p.

Bing, R. Kompendium der topischen Gehirn- und Rückenmarksdiagnostik. 13.Aufl. Basel, Schwabe, 1948, 288 p.

Biochemistry (The) of B vitamins, [by] Roger J. Williams [and others]. New York, Reinhold, [1950], 741 p.

Bumke, O. Gedanken über die Seele. 4.Aufl. Berlin, Springer, 1948, 303 p.

Busse, Grawitz, P. Experimentelle Grundlagen zu einer modernen Pathologie von der Zellular- und Molekularpathologie. Basel, Schwabe, 1946, 359 p.

Callahan, A. Surgery of the eye: injuries. Springfield, Ill., Thomas, [1950], 217 p.

Calmette, A.; Nègre, C. & Boquet, A. Manuel technique de microbiologie et de sérologie. 4.éd. Paris, Masson, 1948, 727 p.

Campos, N. S. & Lima, L. S. Lepra na infancia. Rio de Janeiro, Serviço Nacional de Lepra, 1950, 201 p.

di Cló, A. V. La tensión arterial. 2.ed. Buenos Aires, El Ateneo, 1949, 263 p.

Conference upon the Preservation of the Erythrocytes, Leucocytes, Platelets and Plasma Proteins, Harvard Medical School, 1949. The preservation of the formed elements and of the proteins of the blood. [Proceedings.] [Wash., American National Red Cross, 1949], 339 p.

Dabout, E. & Neveu, R. Petit dictionnaire de médecine. 2.éd. Paris, Baillière, 1949, 739 p.

Daric, J. Vieillissement de la population et prolongation de la vie active. [Paris], Presses Universitaires de France, 1948, 208 p.

Davidoff, L. M. & Dyke, C. G. The normal encephalogram. 3.ed. Phila., Lea, 1951, 240 p.

Davis, M. Facts about the menopause. New York, McGraw-Hill, [1951], 172 p.

Deutsch, A. Our rejected children. Boston, Little, 1950, 292 p.

Dreikurs, R. Fundamentals of Adlerian psychology. New York, Greenberg, [1950], 117 p.

Festschrift Herrn Prof. Dr. E. Rothlin zu seinem 60. Geburtstag gewidmet. [Reprints.] Basel, Schwabe, [1948], 476 p.

Findlay, J. P. Facial paralysis. Sydney, Angus, 1950, 47 p.

Fischer, E. K. Colloidal dispersions. New York, Wiley, [1950], 387 p.

Fluhmann, C. F. Medical treatment in obstetrics and gynecology. Balt., Williams, 1951, 157 p.

Freeman, W. & Watts, J. W. Psychosurgery. 2.ed. Springfield, Ill., Thomas, [1950], 598 p.

Fretz, D. Konrad Gessner als Gärtner. Zürich, Atlantis Verlag, [1948], 312 p.

German aviation medicine, World War II; prepared under the auspices of the Surgeon General, U. S. Air Force. Wash., U. S. Govt. Print. Off., [1950], 2 v.

Gnudi, (Mrs.) M. (Teach) & Webster, J. P. The life and times of Gaspare Tagliacozzi, surgeon of Bologna. N. Y.,

Reichner, [1950], 538 p.

Grollman, A. Pharmacology and therapeutics. Phila., Lea, 1951, 828 p.

Guenther, E. The essential oils, v. 4. New York, Van Nostrand, 1950, 752 p.

Harkness, A. H. Non-gonococcal urethritis. Edinburgh, Livingstone, 1950, 424 p.

Hess, W. R. Das Zwischenhirn: Syndrome, Lokalisationen, Funktionen. Basel, Schwabe, 1949, 187 p.

Hirsch, E. W. Sexual fear. Garden City, Garden City Pub. Co., [1950], 307 p.

Hollinshead, W. H. Functional anatomy of the limbs and back. Phila., Saunders, 1951, 341 p.

Hungerkrankheit, Hungerödem, Hungertuberkulose, von A. Hottinger, O. Gsell, E. Uehlinger [et al]. Basel, Schwabe, 1948, 297 p.

Hunziker, O. F. Condensed milk and milk powder. 7.ed. La Grange, Ill., Author, 1949, 583 p.

Illingworth, C. F. W. & Dick, B. M. A textbook of surgical pathology. 6.ed. London, Churchill, 1949, 726 p.

Ingram, F. L. Radiology of the teeth and jaws. London, Arnold, [1950], 160 p.

Jones, (Sir) Reginald W. and others. Program of the fracture course given at the . . . Lenox Hill Hospital, February . . . 1950. [New York, Ungarsohn, 1950], 282 p.

Jores, A. Klinische Endokrinologie. 3.Aufl. Berlin, Springer, 1949, 428 p.

Keene, (Mrs.) M. F. (Lucas) & Whillis, J. Anatomy for dental students. London, Arnold, [1950], 342 p.

Kiely, P. Text-book of surgery. London, Lewis, 1949, 1184 p.

Kolle, K. Psychiatrie. 3.Aufl. Berlin, Urban, 1949, 443 p.

Kolmer, J. A. Clinical diagnosis by laboratory examinations. 2.ed. New York, Appleton-Century, [1949], 1212 p.

Kretschmer, E. Medizinische Psychologie. 10.Aufl. Stuttgart, Thieme, 1950, 304 p.

Kretschmer, E. Psychotherapeutische Studien. Stuttgart, Thieme, 1949, 215 p.

Lawrence, C. A. Surface-active quarternary ammonium germicides. New York, Academic Press, 1950, 245 p.

Ledoux-Lebard, R. & Ledoux-Lebard, G. R. Manuel de radiodiagnostic clinique. 2.éd. Paris, Masson, 1949, 1407 p.

Lehrbuch der Chirurgie, hrsg. von A. Brunner, C. Henschen, H. Heusser [et al.]. Basel, Schwabe, [1949-1950], 2 v.

Leprince-Ringuet, L. Cosmic rays. New York, Prentice-Hall, 1950, 290 p.

Letters written to Dr. A. J. Carlson by students and friends on the occasion of his seventy-fifth birthday. [Chicago], 1950, 1 v.

Levaditi, C.; Lépine, P. and others. Les ultravirus des maladies humaines. 2.éd. Paris, Maloine, 1948, 2 v.

Lima, L. S. & Campos, N. S. Sôbre casos de lepra com evolução anômala. Rio de Janeiro, Serviço Nacional de Lepra, 1950, 120 p.

Luciani, A. I vizi della mitrale. Pisa, Omnia medica, [1950], 157 p.

McDowall, R. J. S. Handbook of physiology & biochemistry. [40.] ed. London, Murray [1950], 767 p.

Major, R. H. Physical diagnosis. 4.ed. Phila., Saunders, 1951, 446 p.

Mann, I. C. The development of the human eye. [2.ed.] London, Brit. Med. Assoc., 1949, 312 p.

Meessen, H. & Olszewski, J. Cytoarchitektonischer Atlas des Rautenhirns des Kaninchens. Basel, Karger, 1949, 52 p.

Meyer, A. The collected papers. Balt., Johns Hopkins Press, 1950, v. 1.

Mommaerts, W. F. H. M. Muscular contraction. New York, Interscience Publishers, 1950, 191 p.

Myerson, A. Speaking of man. New York, Knopf, 1950, 279 p.

Naegeli, O. Differentialdiagnose in der inneren Medizin. 3.Aufl. Stuttgart, Thieme, 1948, 794 p.

National Research Council. Committee on Survey of Food and Nutrition Research. Survey of food and nutrition research in the United States. [2.ed.] 1948-1949. [Wash., U. S. Govt. Print. Off., 1950], 311 p.

Nesbit, R. M. "Your prostate gland": letters from a surgeon to his father. Springfield, Ill., Thomas, [1950], 50 p.

Pittaluga y Fattorino, G. Vitaminas y sangre. La Habana, Cultural, 1948, 746 p.

Policard, A. Précis d'histologie physiologique. 5.éd. Paris, Doin, 1950, 858 p.

Pye, W. Pye's surgical handicraft . . . edited by H. Bailey. 16.ed. Bristol, Wright, 1950, 724 p.

Read, G. D. The birth of a child; obstetric procedure in normal childbirth. New York, Vanguard Press, [1950], 114 p.

Roussy, G.; Leroux, R. & Oberling, C. Précis d'anatomie pathologique. 3.éd. Paris, Masson, 1950, 1338 p.

Rüst, E. & Ebert, A. Unfälle beim chemischen Arbeiten. 2.Aufl. Zürich, Rascher, 1948, 403 p.

Sanders, B. G. Christianity after Freud. London, Bles, [1949], 157 p.

Schilder, P. F. Psychotherapy. Rev. ed. New York, Bender [1951], 396 p.

Schweitzer, A. Goethe; four studies. Boston, Beacon Press, 1949, 116 p.

Schweitzer, A. The mystery of the kingdom of God. Translated by W. Lowrie. New York, Macmillan, 1950, 174 p.

Scott, G. E. M. Juvenile rheumatism. Melbourne, Ramsay, 1948, 163 p.

Scotti, G. & Sicca, G. T. Le salmonellosi nell'uomo. Pisa, Omnia Medica, [1950], 143 p.

Shattuck, G. C. Diseases of the tropics. New York, Appleton-Century-Crofts, [1951], 803 p.

Shellshear, J. L. & Macintosh, N. W. G. Surveys of anatomical fields. Sydney, Grahme, 1949, 172 p.

Slavson, S. R. Analytic group psychotherapy with children, adolescents and adults. New York, Columbia Univ. Press, 1950, 275 p.

Sliosberg, A. Les algies des amputés. Paris, Masson, 1948, 110 p.

Slotkin, J. S. Social anthropology. New York, Macmillan, 1950, 604 p.

Sobels, J. C. Nutrition de quelques myxomycètes en cultures pures et associées. Gouda [Nederl.], Koch, 1950, 135 p.

Spear, M. R. Keeping idle hands busy; occupational therapy. Minneapolis, Burgess, [1950], 96 p.

Speller, S. R. Law relating to hospitals and kindred institutions. 2.ed. London, Lewis, 1949, 587 p.

Stafford, G. T. Preventive and corrective physical education. Rev. ed. New York, Barnes, 1950, 312 p.

Steincrohn, P. J. How to stop killing yourself. New York, Funk, [1950], 272 p.

Steiner, R. Goethe the scientist. New York, Anthroposophic Press, 1950, 280 p.

Strabismus, ophthalmic symposium (1). Edited by H. Allen. St. Louis, Mosby, 1950, 476 p.

Tassman, I. S. The eye manifestations of internal diseases. 3.ed. St. Louis, Mosby, 1951, 672 p.

Telcky, L. Die Entwicklung der Gesundheitsfürsorge — Deutschland, England, USA. Berlin, Springer, 1950, 142 p.

Therapeutics in internal medicine, edited by F. A. Kyser. New York, Nelson, [1950], 715 p.

Thoma, K. H. Oral pathology. 3.ed. St. Louis, Mosby, 1950, 1592 p.

Thomas, J. E. The external secretion of the pancreas. Springfield, Ill., Thomas, [1950], 149 p.

Titmuss, R. M. Problems of social policy [during World War II]. London, H. M. Sta. Off., 1950, 596 p.

Toxicology of uranium; survey and collected papers, edited by A. Tannenbaum. New York, McGraw-Hill, 1951, 333 p.

Troensegaard, N. A new orientation within protein chemistry. Copenhagen, Munksgaard, 1949, 139 p.

United Nations Relief and Rehabilitation Administration. UNRRA; the history of the United Nations Relief and Rehabilitation Administration. Prepared under the direction of G. Woodbridge. New York, Columbia Univ. Press, 1950, 3 v.

United States. Army. Evacuation Hospital no. 77. Medicine under canvas; a war journal [of the University of Kansas School of Medicine hospital unit]. Kansas City, Mo., Sosland, [1949], 196 p.

United States. Department of Agriculture. Library. List of periodicals currently received in the Library. November 1, 1949. Wash., U. S. Govt. Print. Off., 1950, 349 p.

United States. Office of Scientific Research and Development. National Defense Research Committee. Handbook of aerosols. Wash., [U. S. Govt. Print. Off.], 1950, 147 p.

University of Minnesota. Center for Continuation Study. Continuation course in

otolaryngology, June 26-30, 1950. Minneapolis, [1950], 62 numb. leaves.

University of Rochester. The quarter century; a review of the first twenty-five years, 1925-1950: School of Medicine and Dentistry, Strong Memorial Hospital, Rochester Municipal Hospital. Rochester, N. Y., Univ. of Rochester, 1950, 144 p.

Warburg, O. Heavy metal prosthetic groups and enzyme action. Oxford, Clarendon, 1949, 230 p.

Wees, M. P. & Thornton, F. B. King-doctor of Ulithi. New York, Macmillan, 1950, 128 p.

Weiss, E. Principles of psychodynamics. New York, Grune, 1950, 268 p.

Whitacre, F. E. & Jones, E. W. Maternity care in two counties: Gibson County, Tennessee; Pike County, Mississippi, 1940-41, 1943-44. New York, Commonwealth Fund, 1950, 165 p.

Whitby, L. E. H. & Britton, C. J. C. Disorders of the blood. 6.ed. London, Churchill, 1950, 739 p.

Wiggers, C. J. Physiology of shock. New York, Commonwealth Fund, 1950, 459 p.

Williams, L. H. W. Aids to obstetrics. 12.ed. London, Baillière, 1949, 254 p.

Wishnefsky, N. Antihistamines; industry and product survey. New York, Chemonomics, 1950, 157 p.

Wolff, W. Values and personality; an existential psychology of crisis. New York, Grune, 1950, 239 p.

Woodside, M. Sterilization in North Carolina. Chapel Hill, N. C., Univ. of North Carolina Press, 1950, 219 p.

Wright, G. P. An introduction to pathology. London, Longmans, [1950], 569 p.

Abrikosov, A. I. Osnovy chastnoy patologicheskoy anatomii. [Fundamentals of special pathological anatomy.] 4.izd. Moskva, MEDGIZ, 1950, 471 p.

Ainsworth-Davis, J. C. Essentials of urology. Oxford, Blackwell, [1950], 734 p.

Almeyda, J. V. Major symptoms in clinical medicine. London, Kimpton, 1950, v. 1.

Altschul, R. Selected studies on arteriosclerosis. Springfield, Ill., Thomas, [1950], 182 p.

American Academy of Pediatrics. Maryland Chapter. A study of child health services. [Balt., Furst], 1950, 94 p.

Ars Medici. Diagnostisch-therapeutisches Handbuch. 8.Aufl. mit Ergänzungsband 1944-1947. Liestel [Schweiz], Lüdin, 1948, 2 v. in 1.

Bentley, A. O. A text-book of pharmaceutics. [5.ed.] Rev. by H. Davis. London, Baillière, 1950, 1100 p.

Biemond, A. Diagnostiek van hersenziekten. 2.druk. Haarlem, Bohn, 1950, 595 p.

Blair, V. P. & Ivy, R. H. Essentials of oral surgery. 4.ed. St. Louis, Mosby, 1951, 635 p.

Block, R. J. & Bolling, D. The amino acid composition of proteins and foods. 2.ed. Springfield, Ill., Thomas, [1951], 576 p.

Broman, T. The permeability of the cerebrospinal vessels in normal and pathological conditions. Copenhagen, Munksgaard, [1949], 92 p.

Burn, J. H.; Finney, D. J. & Goodwin, L. G. Biological standardization. 2.ed. London, Oxford Univ. Press, 1950, 440 p.

Carrillo, R. Política sanitária argentina. [Buenos Aires], Ministerio de Salud Pública, 1949, 2 v.

Carter, C. F. Principles of microbiology. St. Louis, Mosby, 1951, 514 p.

Chloupek, D.; Radichev, B. & Richter, B. Malarija. 2.izd. Beograd, 1949, 141 p.

Chobot, R. Pediatric allergy. New York, McGraw-Hill, 1951, 284 p.

Churchill, (Mrs.) S. (Meyers). The adolescent and the family. London, Cresset Press, 1949, 165 p.

Clancy, F. J. Doctor, come quickly! [Autobiography.] Seattle, Superior Pub. Co., [1950], 248 p.

Copper, A. C. An introduction to clinical orbitonometry. Leiden, Stenfert Kroese, 1948, 125 p.

Cox, A. Among the doctors. [Autobiography.] London, Johnson, [1950], 244 p.

Darmbrand, enteritis necroticans, von K. Hansen [et al.]. Stuttgart, Thieme, 1949, 212 p.

Dr. Hugh Auchincloss, 1878-1947 [memorial volume]. [New York, 1950?], 21 p.

Elkin, I. I. & Gandelsman, F. E. Prakticheskie zanyatiya po epidemiologii. [Practical lectures in epidemiology.]

Moskva, MEDGIZ, 1950, 175 p.

Fenczyn, J. Klinika grúzlicy pluc. Krakow, Kolo Medyków Studentow Uniwersytetu Jagiellonskiego, 1948, 320, 95 p.

Fink, D. H. Be your real self. New York, Simon, 1950, 307 p.

Forbes, J. R. & Mann, W. N. Clinical examination of patients, with notes on laboratory diagnosis. London, Arnold, [1950], 323 p.

Glaister, J. Medical jurisprudence and toxicology. 9.ed. Edinburgh, Livingstone, 1950, 755 p.

Goethe, UNESCO's homage on the occasion of the two hundredth anniversary of his birth. [Zurich, Berichthaus], 1949, 179 p.

Gray, J. S. Pulmonary ventilation and its physiological regulation. Springfield, Ill., Thomas, [1950], 82 p.

Greenberg, L. A. Antipyrine; a critical bibliographic review. New Haven, Hillhouse Press, 1950, 135 p.

Gurevich, M. O. Psikhiatriya. [Psychiatry.] Moskva, MEDGIZ, 1949, 501 p.

Gusmão, H. H. Contribução para o estudo do problema da tuberculose nas indústrias de São Paulo. São Paulo, Campanha Nacional contra a Tuberculose, 1950, 158 p.

Hadfield, J. A. Psychology and mental health. London, Allen, [1950], 444 p.

Henry, A. K. The hinge graft or ginglymus implant. Edinburgh, Livingstone, 1950, 64 p.

Höring, F. O. Klinische Infektionslehre. 2.Aufl. Berlin, Springer, 1948, 245 p.

Hoffmann, E. Lebenserinnerungen aus einer Wendezeit der Heilkunde. Hannover, Schmorl, [1948-1949], 2 v.

Hohmann, G. & Jegel-Stumpf, (Frau) L. Orthopädische Gymnastik. 2.Aufl. Stuttgart, Thieme, 1949, 124 p.

Holden, H. M. Noses. Cleveland, World Pub. Co., [1950], 252 p.

Huizinga, E. & Smelt, G. J. Bronchography. Assen, Netherl., Van Gorcum, [1949], 270 p.

Johnson, D. M. A doctor regrets. [Autobiography.] London, C. Johnson, [1949], 242 p.

Jones, J. R. Memories, men and medicine; a history of medicine in Sacramento, California. [Sacramento], Sacramento Soc. for Med. Improv., 1950, 505 p.

Kent, G. H. Mental tests in clinics for children. New York, Van Nostrand, 1950, 180 p.

Kleine, F. K. Ein deutscher Tropenarzt. [Autobiographie.] Hannover, Schmorl, [1949], 182 p.

Knocke, F. J. & Knocke, (Mrs.) L. S. Orthopaedic nursing. Phila., Davis, 1951, 682 p.

Konferencija Epidemiologa, Higijenicara i Bakteriologa Jugoslovenske Armije, Belgrade, 1949. Aktuelni problemi vojne epidemiologije i higijene. Beograd, 1949, 377 p.

Konferencija Hirurga Jugoslovenske Armije, Belgrade, 1948. Iskustva u reparatornoj hirurgiji. Beograd, 1948, 309 p.

Korner, I. N. Experimental investigation of some aspects of the problem of repression: repressive forgetting. New York, Bur. of Publ., Teachers College, Columbia Univ., 1950, 60 p.

Krasilnikov, N. A. Opredelitel bakteriy i aktinomitsetov. [Classification of bacteria and actinomyces.] Moskva, Izd. Akad. Nauk SSSR, 1949, 829 p.

Langer, E. Atlas der Syphilis. Berlin, Berliner mediz. Verlagsanst., [1949], 36 p. 53 plates.

Larsell, O. Anatomy of the nervous system. 2.ed. New York, Appleton-Century-Crofts, [1951], 520 p.

Leff, S. The health of the people. London, Gollancz, 1950, 288 p.

Likhachev, A. G.; Preobrajenskiy, B. S. & Temkin, Y. S. Bolezni ukha, nosa i gorla. [Diseases of the ear, nose and throat.] 4.izd. Moskva, MEDGIZ, 1950, 483 p.

Lowrey, L. G. Psychiatry for social workers. 2.ed. New York, Columbia Univ. Press,]1950[, 385 p.

McCurdy, R. N. C. The rhesus danger; its medical, moral and legal aspects. London, Heinemann, 1950, 138 p.

McDonald, J. J.; Chusid, J. G. & Lange, J. Correlative neuroanatomy. 5.ed. Palo Alto, Calif., Univ. Medical Publishers, [1950], 180 p.

Meader, C. L. & Muyskens, J. H. Hand-

book of biolinguistics, pt. 1a. Toledo, O., Weller, 1950, 330 p.

Meijer, F. G. D. Over de anaerobe omzetting van pyrodruivenzuur. Deventer-Djakarta, Kluwer, [1950], 96 p.

Meyer, H. H. Der Liquor; Untersuchung und Diagnostik. Berlin, Springer, 1949, 193 p.

National Research Council. Committee on American Scientific and Technical Bibliography. Scientific, medical, and technical books. . . . Supplement of books published 1945-1948. Wash., 1950, 514 p.

Oettel, H. Degenerative Nierenerkrankungen. Leipzig, Thieme, 1948, 328 p.

Osborne, S. L. Diathermy; the use of high frequency currents. Springfield, Ill. Thomas, [1950], 113 p.

Pattison, H. A. Rehabilitation of the tuberculous. [3.ed.] Livingston, N. Y., Livingston Press, [1949], 250 p.

Pi Suñer, A. The bridge of life; from reality to mystery. New York, Macmillan, 1951, 270 p.

Predtechenskiy, V. E.; Borovskaya, V. M. & Margolina, L. T. Rukovodstvo po laboratornym metodam issledovaniya. [Handbook of laboratory methods of clinical research.] 4 izd. Moskva, MEDGIZ, 1950, 803 p.

Schnohr, E. Thorkild Rovsing. København, Gaardbroder-Samfund, 1948, 174 p.

Schönfeld, W. & Kimmig, J. Sulfonamide and Penicilline. Stuttgart, Enke, 1948, 327 p.

Schubert, G. E. & Beyer, G. P. H. Die chirurgische Stationsarbeit. Leipzig, Thieme, 1949, 320 p.

Schultz-Hencke, H. Lehrbuch der Traumanalyse. Stuttgart, Thieme, 1949, 283 p.

Scientific research: its administration and organization. Edited by G. P. Bush and L. H. Hattery. Wash., Amer. Univ. Press, [1950], 190 p.

Segal, M. S. The management of the patient with severe bronchial asthma. Springfield, Ill., Thomas, [1950], 158 p.

Sherman, H. C. The nutritional improvement of life. New York, Columbia Univ. Press, 1950, 270 p.

Siebeck, R. Medizin Bewegung; klinische Erkenntnisse und ärztliche Aufgabe. Stuttgart, Thieme, 1949, 320 p.

Simkins, C. S. Functional human anatomy. Dubuque, Ia., Brown, [1949], 593 p.

Simpson, G. G. The meaning of evolution. New Haven, Yale Univ. Press, [1950], 364 p.

Spearman, C. E. & Wynn Jones, L. Human ability. London, Macmillan, 1950, 198 p.

Stoker, W. C. & Seifert, W. W. "Shielding for diathermy". Troy, N. Y., Rensselaer Polytechnic Inst., 1949, 61 p.

Storch, C. B. Fundamentals of clinical fluoroscopy. New York, Grune, 1951, 196 p.

Struthers, J. A. Aids to sanitary science and law. 4.ed. London, Baillière, 1949, 380 p.

Sturm, A. Die klinische Pathologie der Lunge in Beziehung zum vegetativen Nervensystem. Stuttgart, Wissenschaftl. Verlagsges., 1948, 352 p.

Symposium on Copper Metabolism, Johns Hopkins University, 1950. Copper metabolism. Balt., Johns Hopkins Press, 1950, 443 p.

Taschenbuch der praktischen Medizin. Hrsg. von J. Kottmaier. Stuttgart, Thieme, 1949, 790 p.

Ultraschall (Der) in der Medizin, v. [1]-2. Zürich, Hirzel, 1949-1950, 2 v.

United States. Army Medical Library. The pituitary-adrenocortical function: ACTH, cortisone and related compounds; a bibliography. Wash., 1950, 366 p.

Walter, J. & Miller, H. A short textbook of radiotherapy. London, Churchill, 1950, 444 p.

Watson, F. Dawson of Penn. London, Chatto, 1950, 344 p.

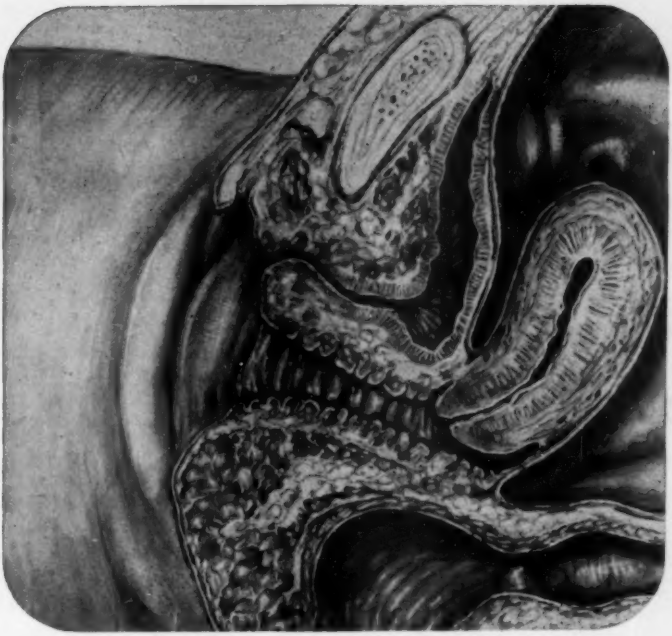
Wilkins, L. The diagnosis and treatment of endocrine disorders in childhood and adolescence. Springfield, Ill., Thomas, [1950], 384 p.

Williams, H. E. Humanizing our great profession [dentistry]. Red Bank, N. J., Williams, 1949, 288 p.

Wilton, G. How to overcome stuttering. New York, Harper, [1950], 168 p.

Wittkower, E. A psychiatrist looks at tuberculosis. London, Nat. Assoc. for the Prev. of Tuberc., 1949, 151 p.

Zeegers, M. Ziekten van de geest. Baarn [Nederl.], Bosch, [1949?], 312 p.



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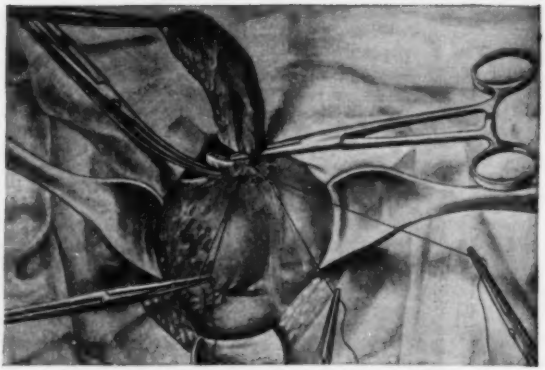

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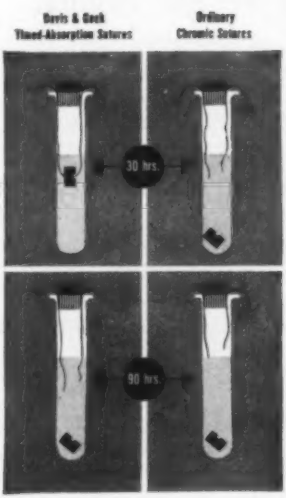

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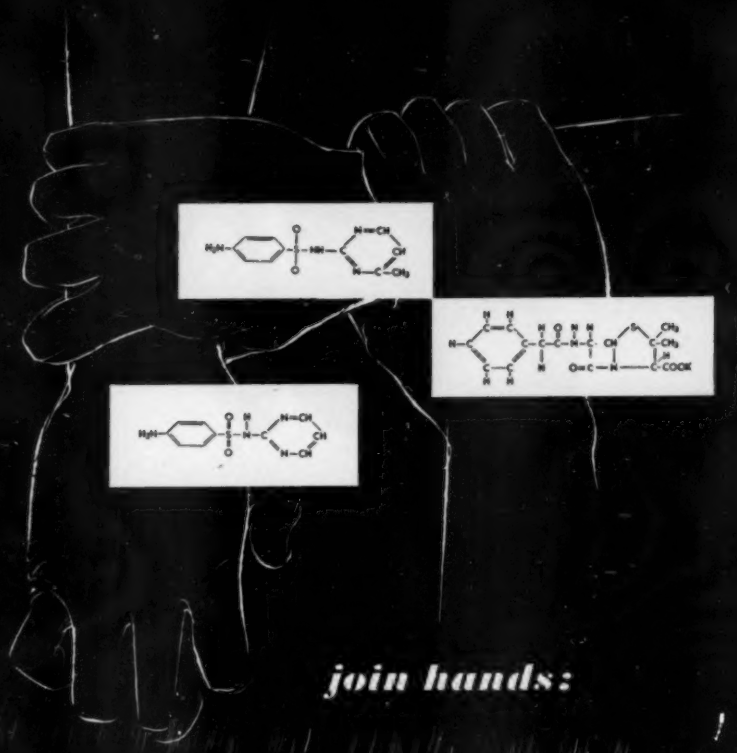

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In vitro and in vivo studies clearly demonstrate that in combating a wide range of organisms, penicillin, the *antibiotic* of greatest use, and the *sulfas* "join hands". To widen both antibacterial spectrum *and* effectiveness,

simply Rx **Biosulfa***

Each tablet contains:

Penicillin G Potassium, Crystalline	100,000 units
Sulfadiazine	0.25 Gm.
Sulfamerazine	0.25 Gm.
Calcium Carbonate	4 grs.

Available in bottles of 50 tablets.

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PRECALCIN®
CAPSULES

Lactation

PATIENT-ACCEPTANCE assured because the colorful two-tone, easy-to-swallow capsules, plus the dry powder "fill", make PRECALCIN continuously agreeable to all patients. There is no fish-oil aftertaste.

DOSAGE: 1 PRECALCIN Capsule three times daily, or more as prescribed.

AVAILABLE: Bottles of 100, 500, and 1,000 capsules.

Each capsule contains:

Dicalcium Phosphate (Anhydrous)	0.45 Gm.
Bone Phosphate*	0.15 Gm.
Vitamin A (Ester)	2,000 U.S.P. Units
Vitamin D (Irradiated Ergosterol)	400 U.S.P. Units
Thiamine Hydrochloride	3.00 mg.
Riboflavin	2.00 mg.
Niacinamide	10.00 mg.
Ascorbic Acid	30.00 mg.
Ferrous Gluconate	45.00 mg.
*Fluorine content	0.07 mg.

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Interchangeable and Equally Effective

Oral

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Clinical studies have demonstrated that the therapeutic activity of Cortone* is similar whether administered parenterally or orally. Dosage requirements are approximately the same, and the two routes of administration may be used interchangeably or additively at any time during treatment.

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Literature on Request

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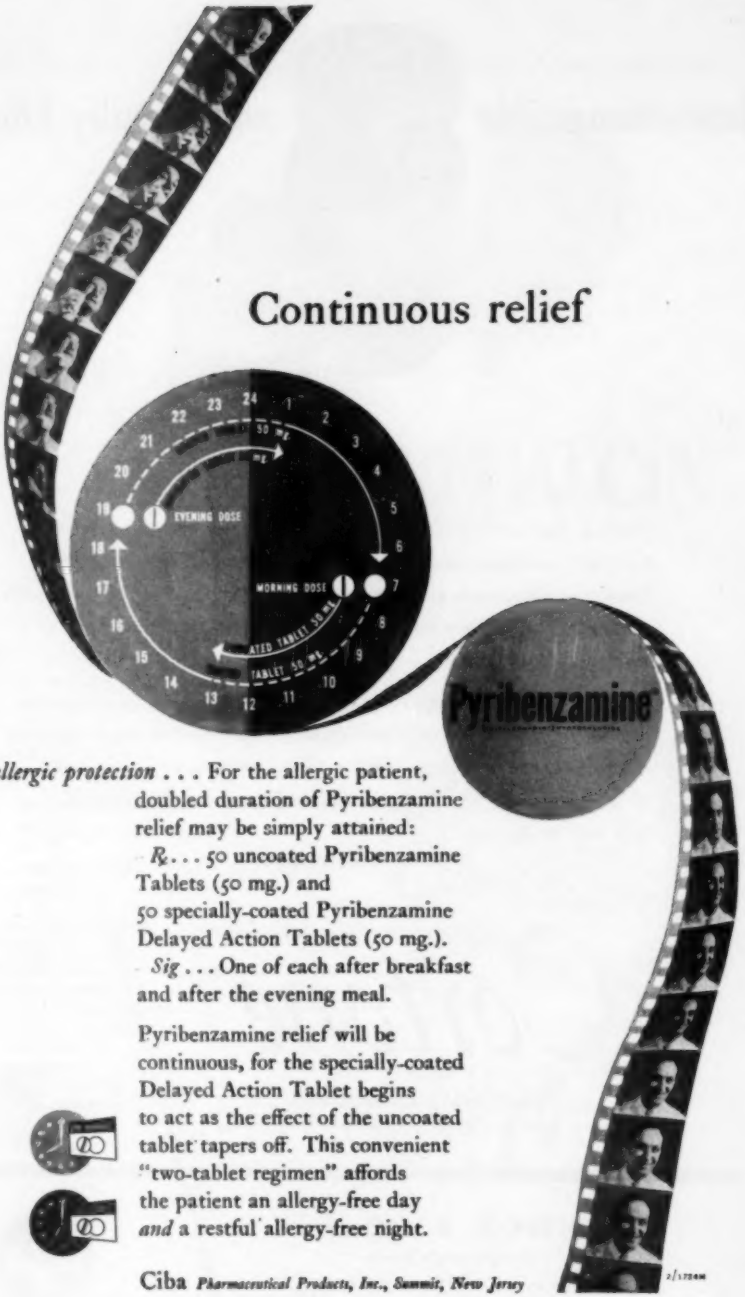

24-hour allergic protection . . . For the allergic patient, doubled duration of Pyribenzamine relief may be simply attained:

℞ . . . 50 uncoated Pyribenzamine Tablets (50 mg.) and 50 specially-coated Pyribenzamine Delayed Action Tablets (50 mg.).

Sig . . . One of each after breakfast and after the evening meal.

Pyribenzamine relief will be continuous, for the specially-coated Delayed Action Tablet begins to act as the effect of the uncoated tablet tapers off. This convenient "two-tablet regimen" affords the patient an allergy-free day *and* a restful allergy-free night.

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for supplemental and prophylactic use

For many years, much time and effort has been given to the development of an effective multivitamin preparation which would not frighten or repel the patient by its size, disagreeable taste or odor, and unpleasant appearance. The stability of OMNI-VITA* Spherettes is assured by layering of the vitamin components. Younger patients and finicky adults, particularly, were likely to object strenuously to the average multivitamin preparation—oils, liquids, tablets, or capsules.

Warner is proud, therefore, to present OMNI-VITA* Spherettes. A delicious, chewable Spherette containing generous amounts of the vitamins—an excellent and extremely convenient means for supplying either supplemental or prophylactic doses of the vitamins most frequently low in the modern diet or involved in subclinical deficiencies.

OMNI-VITA* Spherettes have a full and balanced complement of vitamins. Each Spherette contains:

Vitamin A, Synthetic	5,000 U.S.P. Units	Vitamin B_2 (Riboflavin)	2.0 mgs.
Vitamin D (Activated Ergosterol)	1,000 U.S.P. Units	Vitamin B_6 (Pyridoxine Hydrochloride)	0.5 mg.
Vitamin C (Ascorbic Acid)	50.0 mgs.	Vitamin B_{12}, Crystalline	1.0 mcg.
Vitamin B_1 (Thiamine Hydrochloride)	1.0 mg.	Panthenol (equiv. to 1.15 mgs. d-Calcium Pantothenate)	1.0 mg.

The supplemental or prophylactic use of OMNI-VITA* Spherettes ensures the the patient's cooperation—children and adults alike.

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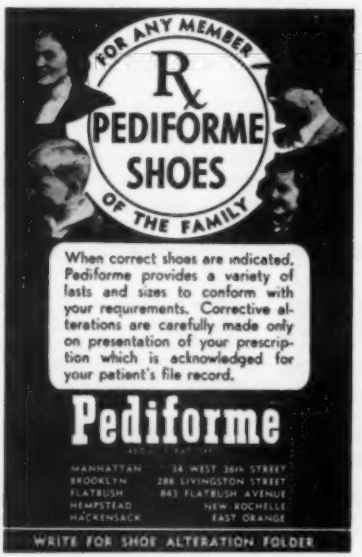
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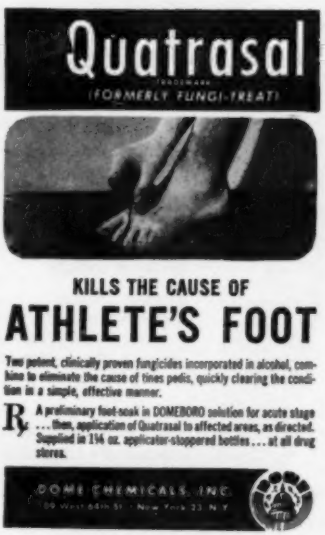
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(for prompt action)

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(for delayed action)

One capsule and one tablet, taken at bedtime will provide almost all patients with eight hours relief and sleep. The relief can be sustained by using the capsules during the day at 4 hour intervals as required.

Each capsule and enteric-coated tablet contains:

Theophylline Sodium Acetate	(3 gr.) 0.2 Gms.
Ephedrine Sulfate	(½ gr.) 30 Mg.
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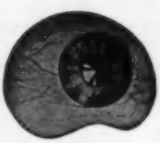

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"In general, symptomatic improvement [of menopausal symptoms] was striking within 7 to 14 days after treatment..." with "Premarin."

Gray, L.: J. Clin. Endocrinol. 3:92 (Feb.) 1943.

Many clinicians have found that "Premarin" therapy usually brings about prompt relief of distressing menopausal symptoms. Furthermore, symptomatic improvement is followed by a gratifying sense of well-being in a majority of cases. This is the "plus" in "Premarin" therapy which tends to quickly restore the patient's normal mental outlook.

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℞ ½ or 1 Quadrinal Tablet every 3 or 4 hours, not more than three tablets a day.

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Quadrinal Tablets are marketed in bottles of 100, 500 and 1000.

Quadrinal, Phyllicin. Trademarks E. Bilhuber, Inc.

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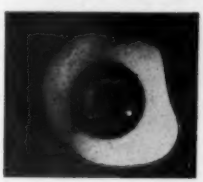

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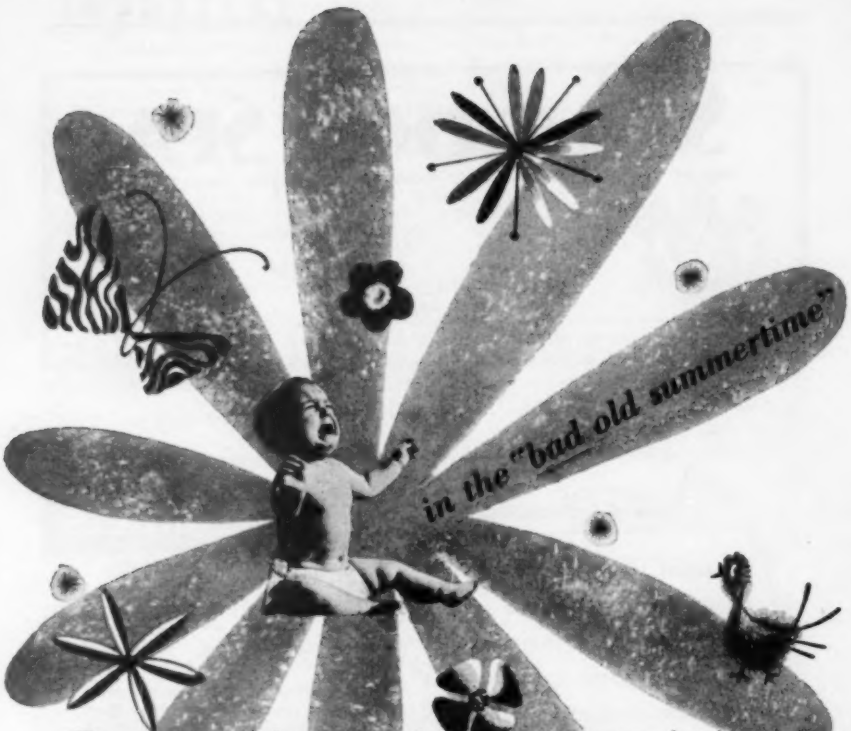

The expression *Cholera infantum* is with the yesteryears—but fermentative diarrhea is with us still, especially in the "bad old summertime."

For the successful management of this syndrome, many physicians rely on Dryco. Because of its low-fat and low-carbohydrate to high-protein ratio, Dryco is well adapted to the impaired digestive capacity of the infant...the fine, flocculent curd is readily digested. Dryco is enriched with vitamin A and vitamin D. Only vitamin C need be added in the diet.

For the very next case of summer diarrhea you encounter, prescribe Dryco. Dryco is frequently used for supplemental feeding. Each tablespoonful will supply 31½ calories. Dryco is readily reconstituted in cold or warm water. Available at pharmacies in 1 and 2½ lb. cans.

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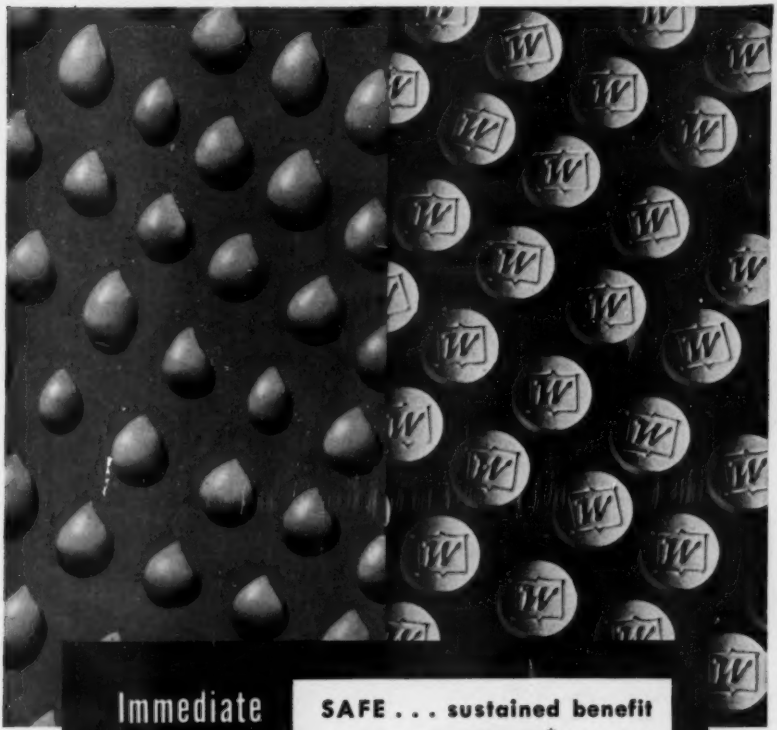

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no acid rebound

SAFE . . . sustained benefit

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Swallow—do not chew. Disintegrates and dissolves rapidly in gastric juice.

Prescribe either
A-M-T SUSPENSION: Bottles of 12 fl. oz.
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greater effectiveness . . .

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In an evaluation of available antihistaminic agents[1] it was stated:

"There is still a need for drugs which possess more consistent action against histamine and which produce less toxic side effects."

The search has continued for a more potent and better tolerated antihistaminic.

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Supplied in tablets of 15 mg., bottles of 100.

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For symptomatic or palliative treatment of hay fever, perennial rhinitis, bronchial asthma, urticaria, contact and atopic dermatitis (allergic eczema) and other forms of allergy.

1. Modern Concept of Allergy and Drugs Used in Its Control. *Med. Times.* 75:256. Sept., 1947.
2. Lands, A.M., Hoppe, J.O., Hegmann, O.H., and Ludueña, F.P.: *Jour. Pharmacol. & Exper. Therap.*, 95:45, Jan., 1949.
3. Ludueña, F.P., and Anzenko, E.: *Jour. Allergy*, 20:434, Nov., 1949.
4. Clinical investigations (unpublished) reported to Department of Medical Research, Winthrop-Stearns Inc.

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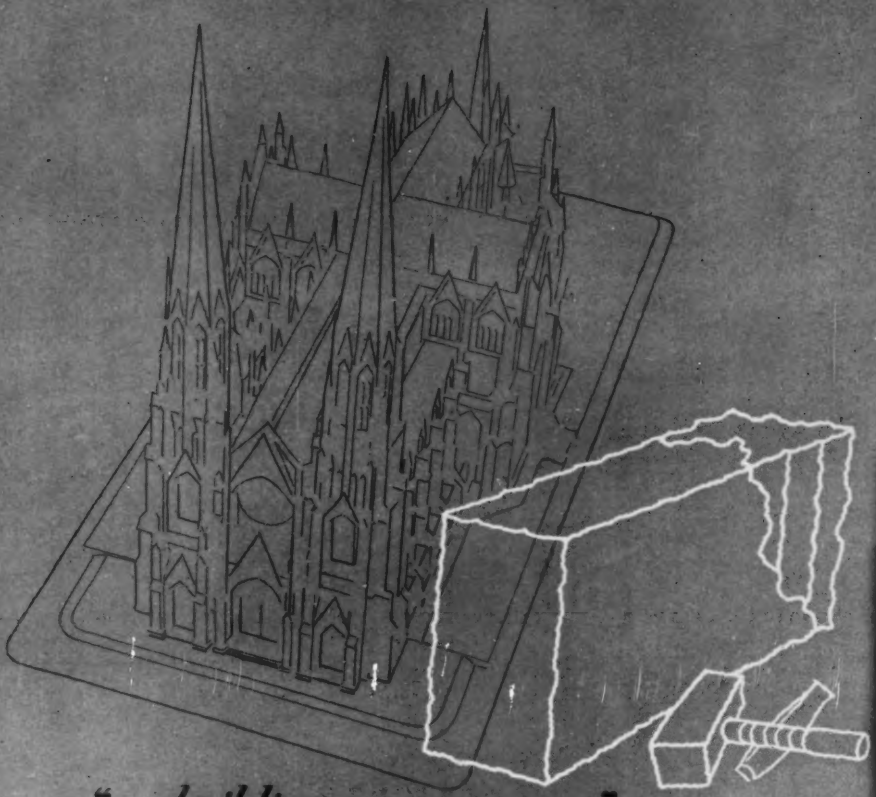

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A philosopher stood watching three stonecutters and of each in turn he asked: "What are you doing?" The first said: "I am cutting stone." The second: "Why, I am earning a dollar an hour!" The third said quietly: "I am building a Cathedral."

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Lipotropic therapy in 115 patients with proved coronary occlusion and myocardial infarction, over a period of one to three years, led to a significant reduction in mortality as compared with an untreated control group of 115 patients with the same diagnosis.

—Morrison, L. M. and Gonzales, W. F.: Am. Heart J., 38:471 (Sept. 1949).

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